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Lupus, Sjogren's and Overlap : Apparently same or Distinctly Different?

Prof. Rohini Handa*

Connective tissue diseases (CTDs) are characterised by remarkable heterogeneity on a background of considerable uniformity. Features common to CTDs include multisystem involvement, arthritis, rash, Raynaud's phenomenon, serositis, sicca features, myocarditis etc. along with one or more autoantibodies, notably the antinuclear antibodies (ANA). Despite being characteristic, these findings are not pathognomonic of any one disease. However, the unique clustering of these findings permits classification into different diseases that comprise the spectrum of CTDs like systemic lupus erythematosus (SLE), systemic sclerosis, Sjogren's syndrome (SS), dermatomyositis etc. This also necessitates the application of classification criteria, an abundance of which exists in Rheumatology.

Nature being nature, the CTDs do not always exist in isolated splendour. Overlap syndromes are common and some of these syndromes are associated with a distinct autoantibody signature like the presence of u1RNP antibodies in mixed connective tissue disease. The clinical coexistence of SLE and SS was recognized several decades ago.¹ The prevalence of SS among patients with SLE varies from 8-30% and it has been suggested that in patients with SLE-SS, the associated lupus appears to be relatively more benign, and that these patients exhibit a relatively increased frequency of autoantibodies to Ro/SSA

and La/SSB.^{2,3} Pradhan and colleagues in this issue of the Assam Journal of Internal Medicine report their experience with SLE overlap with Sjogren's syndrome.⁴ Their experience is in keeping with the literature available worldwide.

Given the context of overlaps, a clinician should aim to delineate the organ involvement in every patient with CTD irrespective of the diagnostic label. This involves a thorough physical examination and judicious use of investigations. Urinalysis is a very important but underutilized investigation. All patients with CTD require periodic urinalysis to detect proteinuria/hematuria suggestive of renal involvement which is usually asymptomatic but has a major bearing on prognosis. Therapy is directed according to organ involvement. For example, the arthritis of a CTD, whether SLE, Sjogren's syndrome or overlap syndrome would be treated with the same DMARDs like hydroxychloroquine or methotrexate. Treatment decisions should also never be postponed or delayed pending classification.⁵

From a clinical perspective, it is important to appreciate that all possible permutations and combinations can be encountered with autoimmune rheumatic diseases. This is what makes CTDs fascinating and challenging at the same time. The delineation of organ involvement is more important than labels since this influences treatment. Clinicians should refrain from floundering in semantic depths or nosologic debates. The focus ought to be on the patient rather than descriptive labels.

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Overlap of Sjogren's Syndrome with Systemic Lupus Erythematosus : A Report from Western India

V Pradhan*, A Rajadhyaksha**, M Patwardhan***, P Pandit****, P Surve*****, K Ghosh*****

Abstract

Background: Systemic Lupus Erythematosus (SLE) is one of the most closely related autoimmune disease to secondary Sjogren's syndrome (sSS), not only due to their frequent coexistence, but also due to the significant overlap in their clinical and immunological expression. **Objective :** To investigate clinical presentation and autoantibody profile of Sjogren syndrome overlap associated with SLE patients from Western India. **Methods:** Fifty SLE patients having an overlap of sSS (SLE-sSS) and 50 SLE without sSS patients were included. All patients were clinically diagnosed using the American College of Rheumatology (ACR) criteria for SLE. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Clinical and laboratory characteristics were noted at the time of evaluation. Autoantibodies like ANA and anti-dsDNA were detected by Indirect Immunofluorescence test (BioRad Laboratories, USA). Other ANA specificities were tested by ANA-BLOT (Euroimmune, Lubeck). **Results:** In SLE-sSS patients 60% showed sicca syndrome, 54% had arthritis, 24% had photosensitivity, 22% had oral ulcers, 16% had serositis, 8% had neurological disorders and 8% patients had hematological manifestations. SLE without sSS showed significantly higher incidence of renal disorder ($p=0.0262$), Oral ulcers ($p=0.0193$). SLE-sSS patients showed higher incidence of Anti-SSA (Ro) and Anti-SSB (La) ($p<0.001$). **Conclusion:** SLE patients with Secondary overlap of Sjogren Syndrome showed different clinical presentation and autoantibody profile compared with SLE without Secondary Sjogren Syndrome.

KEY WORDS : Secondary Sjogren's syndrome (sSS), Systemic Lupus Erythematosus (SLE), overlap, autoantibodies

INTRODUCTION :

Sjogren's syndrome (SS) is a chronic, progressive autoimmune disease primarily affecting women. Diagnosis of SS requires an invasive salivary gland tissue biopsy and a long delay from the start of the symptoms to final diagnosis has been frequently observed. The prevalence of SS among patients with SLE varies considerably among the published studies (from 8% to 30%). These studies have indicated that in patients with SLE-sSS, the

associated lupus appears to be relatively more benign, and that these patients exhibit a relatively increased frequency of autoantibodies to Ro/SSA and La/SSB RNPs.¹ Anti-SSA(Ro) antibodies have the most prevalent specificity among many autoimmune diseases, such SLE, Sjogren's Syndrome overlap among SLE patients (SLE-sSS), subacute cutaneous LE (SCLE) and neonatal SLE.² In contrast, anti-SSB (La) antibodies more associated with primary Sjogren's syndrome (SS). However, these studies are limited and the expression of SS that coexists with SLE needs to be further addressed.

In Systemic Lupus Erythematosus (SLE) and Sjogren's syndrome (SS) autoantibodies mainly target multi component ribonucleoprotein (RNP) complex SSA (Ro) and/or SSB (La). The anti-SSA (Ro) and/or anti-SSB (La) system is considered as a heterogeneous antigenic complex, constituted by three different proteins (60 kDa Ro, 52 kDa Ro and La) and four small RNAs particles. The differences between these antigens further explain why the common antigenic specificities are not shared by them

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for development of respective autoantibodies.³ The association of a 52 kDa protein with SSA/Ro antigen was described later and it is thought to associate with the complex via the 60 kDa protein. No sequence homology exists between the 52 kDa and 60 kDa proteins. Whether the Ro52 kDa protein is permanently associated with SSA (Ro) ribonucleoprotein (RNP) or not, and to which cellular compartment of Ro52 kDa protein is located are still not known.^{4,5} This study was aimed to investigate the clinical presentation and autoantibody profile of Sjögren syndrome overlap associated with SLE patients (SLE-sSS) from Western India to understand whether this coexistence modifies disease severity.

MATERIAL AND METHODS:

SLE patients were clinically diagnosed according to the American College of Rheumatology (ACR) criteria.⁶ This study was carried out after obtaining requisite Institute Ethics Committee (IEC) approval and after obtaining written consent from patients. Disease activity was assessed at the time of evaluation by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).⁷ All the patients diagnosed SLE-sSS patients included in the study were further confirmed by schirmer's test along with the subjective manifestation of sicca syndrome. Pregnant and post menopausal women, smokers, patients with diabetes and patients with significant hyperlipidemia were excluded. After blood collection, sera were stored in aliquots at -80°C until tested. Anti-Nuclear antibodies (ANA) were detected using Hep-2 cells and anti-dsDNA antibodies were detected using Crithidia luciliae as substrate (BioRad laboratories, USA) by indirect immunofluorescence test using a fluorescent microscope (Nikon, Optiphot II, Japan). Other ANA specificities were detected using ANA profile 3 EUROLINE kits (Euroimmune, Lubeck). The laboratory was blinded to the disease status of patients and their visceral involvement and a double blinded study was conducted on the autoantibody positive samples.

RESULTS:

The mean age at evaluation of SLE-sSS patients studied was 10 - 70 years (mean±SD; 29.9 ± 11.4). Age at onset of the disease ranged between 10 - 70 years (mean±SD; 27.1 ± 10.8). The SLEDAI scores ranged between 4 - 24 (mean±SD; 12.8 ± 6.8). It was observed

Table 1: Autoantibody profile in SLE-SS patients studied (n=50)

Autoantibodies	Number positives	Percentage positivity
ANA	50	100 %
Anti-dsDNA	44	88%
Anti-SSA (Ro)	50	100 %
Anti-Ro 52	26	52 %
Anti-SSB (La)	10	20 %
Anti-nRNP	23	46 %
Anti-Sm	20	40 %
Anti-Scl 70	10	20 %
Anti-Rib P	07	14 %
Anti-Nucleosome	06	12 %
Anti-histone	04	8 %
Anti-CENP B	02	4 %
Anti-Mitochondrial (AMA)	02	4 %
Anti-PCNA	01	2 %

that 30/50 patients (60%) had malar rash, 30/50 patients (60%) had sicca syndrome, 27/50 patients (54%) had arthritis, 12/50 patients (24%) had photosensitivity, 11/50 patients (22%) had oral ulcers, 8/50 patients (16%) had serositis, 4/50 patients (8%) had neurological disorders and 4/50 patients (8%) had hematological disorders such as leucopenia, thrombocytopenia and autoimmune hemolytic anemia (AIHA). It was noted that 16/50 patients (32%) had renal disorders and they were grouped as lupus nephritis (LN) where as remaining 34 patients (68%) having no renal involvement were grouped as nonLN.

Anti-nuclear antibody (ANA) positivity was 100% and anti-dsDNA antibodies were present in 88% SLE-sSS patients. Table 2 gives details of other autoantibody profile in SLE-sSS patients studied. It was observed that SLE-sSS patients showed an incidence of anti-SSA (Ro) was 100 %, anti-SSB (La) antibodies were present in 10/50 patients (20%). The incidence for other ANA specificities showed an incidence of anti-nRNP (30 %), anti-Sm (24%), anti-Rib P (12%), anti-nucleosome (12%). A lower incidence was noted for anti-Scl70 (10%), anti-

Table 2 : An association of other ANA specificities among SLE-SS patients with multiple specificities for anti-SSA, anti-Ro52 and anti-SSB antibodies.

ANA specificities	Anti-SSA alone (n=19)	Anti-SSA+ anti-Ro52 (n=21)	Anti-SSA+ anti-SSB (n=5)	Anti-SSA+ anti-Ro52 + anti-SSB(n=5)
Anti-dsDNA	10	14	3	3
Anti-Nucleosome	3	3	0	0
Anti-Histone	2	2	0	0
Anti-nRNP	9	10	2	2
Anti-Sm	9	8	1	2
Anti-Scl 70	5	2	0	1
Anti-Rib P	3	3	0	1
Anti-Mitochondrial	1	0	0	1
Others (anti-PM/Scl, anti-Jo1, anti-CENP B, anti-PCNA)	1	1	0	0

Table 3 : Distribution of multiple specificities for anti-SSA, anti-Ro52 and anti-SSB antibodies among LN and nonLN patients.

SLE type	Anti-SSA alone (n=19)	Anti-SSA+ anti-Ro52 (n=21)	Anti-SSA+ anti-SSB (n=5)	Anti-SSA+ anti-Ro52 + anti-SSB (n=5)
LN (n= 20)	8 (40%)	9 (45 %)	2 (10%)	1 (5%)
Non-LN (n=30)	11 (36.7%)	12 (40%)	3 (10%)	4 (13.3%)

histone (10%), anti-mitochondrial antibodies (AMA) 4% and anti-CENP B (0%), anti-PCNA antibodies were absence among SLE-sSS patients.

DISCUSSION:

Significant association and an increased evidence of direct involvement of anti-SSA(Ro) and anti-SSB (La) autoantibodies in the pathogenesis of tissue injury in SLE had been reported.⁸ Our earlier report had shown an increased incidence of anti-SSA(Ro) with skin, kidney and sicca syndrome among anti-dsDNA positive patients where as among patients that had both anti-SSB(La) antibodies and anti-dsDNA antibodies, clinical manifestations such as skin rash, renal involvement, sicca syndrome, serositis and Raynaud's phenomenon was more commonly associated. Among patients having both anti-SSA (Ro) and anti-SSB (La) autoantibodies, skin manifestations were the most prominent features.⁹

Gilboe et al had reported association of sicca syndrome with a higher frequency of fatigue and anti-Ro (La) antibodies and a lower frequency of renal involvement in SLE-sSS patients.¹⁰ Our study also reported similar results (32%) in SLE-sSS v/s 54% in SLE without sSS (p=0.0262). Anti-Ro (La) antibodies were exclusively present in SLE-sSS patients. Manoussakis et al had reported a higher frequency of fatigue and thrombocytopenia, Raynaud's phenomenon, arthritis and dyspareunia were more common among SLE-sSS patients than patients with primary SS.¹¹

In our study oral ulcer (p=0.0193) were most prevalent among SLE-sSS patients which supported the findings by Hernandez-Molina G et al¹². Dryness of mouth with oral ulcers noticed in these patients were associated with the presence of autoantibodies to SS-A/SS-B.

The incidence of SS-A/SS-B reported in the present study had limitations to explain the clinical relevance of these autoantibodies. Due to lack of differences in clinical symptoms in SLE-sSS patients at evaluation as compared with non SLE-sSS group. Follow-up study in these patients

with specific markers of SS would further throw light on the subsequent association of SS-A/SS-B autoantibodies.

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Assessment of Thrombolytic Affect of the Recombinant Tissue Plasminogen Activator in Acute STEMI Patients in TMC Hospital

A Datta*, A K Bhattacharyya**

Abstract

Objective : To assess the thrombolytic affect of the recombinant tissue plasminogen activator (Reteplase) in acute STEMI patients along with its adverse affects. **Patients And Methods:** Twenty four acute STEMI patients who were admitted and treated with Reteplase as thrombolytic following confirmation of the diagnosis and proper consent comprised the materials of this retrospective study. Along with thrombolysis all the patients were treated with Aspirin, Clopidogrel, Statins, Low molecular weight heparin and all other supportive treatments. The patients were closely followed up and serial ECGs were taken at different intervals and noted. Any adverse affect following thrombolysis also were noted. Once the patients recovered they were discharged after seven days and followed up upto 30th day. **Results:** In this study, males were predominant(91.66%) with average age of 54±11.72years. There were 54.16% hypertensive, 29.1% diabetic, 58.3% smoker, 12.5% alcoholics and 4.16% patients had family h/o CAD. 95.83% patients were dyslipidemic. 58.33% patients had anterior wall MI, others had inferior wall involvement. Mean duration of symptom, mean time to initiate thrombolysis and average time required for affective thrombolysis were 176.66±80.33mins, 229.92±13.96 mins and 95.45±28.07 mins respectively. Mortality rate and overall bleeding complication were 8.33% with major bleeding episode being 4.16%.

KEY WORDS : Recombinant tissue plasminogen activator(Reteplase), Acute ST elevated myocardial infarction, thrombolysis.

INTRODUCTION:

Acute ST segment elevation myocardial infarction (STEMI) is a leading cause of mortality all over the world¹. Primary Angioplasty in acute myocardial infarction is proven all over the world as the gold standard of treatment by way of establishing high percentage of reperfusion and complete reperfusion (TIMI3goal, TMP and TFC score)². But this treatment modality is available to <10% STEMI patients in India as of today . Even in USA 28%of STEMI get PAMI ,and this percentage is higher in European countries with good transfer facility².

Although PCI has been shown to provide more complete and sustained reperfusion than thrombolysis, thrombolytic therapy still remains most commonly used reperfusion therapy all over the world,³ especially in

regions, where PCI is not feasible and particular in first 3hrs of acute MI where the more prompt reperfusion with thrombolytics may balance the superiority of PCI. Optimal thrombolytic therapy in acute MI must aim to achieve early and complete reperfusion of infarct related coronary artery and establishment of normal coronary flow (TIMI grade 3) is the key correlate of improved survival⁴.

Reteplase is a potent thrombolytic agent which is widely used in the management of acute myocardial infarction and stroke. It belongs to the 3rd generation of thrombolytic drugs and has been delivered from native human tissue plasminogen activator by removing three domains of it and keeping the Krige 2 and serine protease domain⁵.

Among the thrombolytic agents available reteplase has been shown to be superior than streptokinase in regard of establishment of TIMI-3 score at 90 min after thrombolysis (55-60% to 32) and also regarding the side effects¹.

In an institution like TMC & Dr.BRAM Teaching Hospital in Tripura, India where PCI facility is not available thrombolytics remain the mainstay of treatment and among the thrombolytics Reteplase can be better choice in this purpose.

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Correspondence Address : Arindam Datta, Associate Professor, Department of Medicine, TMC& Dr. BRAM Teaching hospital

PATIENTS AND METHODS :

This study was conducted in TMC & Dr.BRAM Teaching Hospital Hapania,Agaratala for the period of 2(two) years from January 2012 to December 2013. This is a retrospective study where information was collected from the database and records are analysed. 24 STEMI patients during these 2 years period who were treated in ICCU of TMC with consent to get treated with Reteplase were included in this study. Patients who had contraindication for thrombolysis like history of active bleeding, recent bleeding episode, recent h/o haemorrhagic CVA, history of bleeding dyscrasia, history of hepatic disease were excluded in this study. From the history, presence of any risk factor like hypertension, Diabetes mellitus, smoking, alcoholism, dyslipidemia, family history of coronary artery diseases also noted.

Once the diagnosis of STEMI has been established by clinical features, ECG and positive cardiac biochemical markers, either troponin –T or CK(MB) or both and all the formalities completed, the patients were injected 2 bolus doses of Reteplase each of 10 units IV for 02 mins with 30 mins apart. During this period patients were closely observed for any complication like bleeding episodes, or any unwanted incidents. Cardiac monitors were there to monitor ECG changes as well as surface ECG were taken before, during and first after the thrombolysis and also at 60 mins & 90 mins after thrombolysis and changes in ECG were observed and noted. The time duration for affective thrombolysis as evidenced by 50% reduction of ST elevation or appearance of ill sustained ventricular tachycardia was also noted. All the patients were given bolus dose of Aspirin(300 mg), clopidogrel(300mg) and atorvastatin (80mg) prior to thrombolysis . All the patients were provided low molecular weight heparin along with thrombolysis for 7 days along with Aspirin(150mg), Clopidogrel(75mg) and Atorvastatin(80mg) everyday. The patients were observed for 7 days in the hospital and if no complication was there, were discharged with proper advice and followed up upto 30 days.

STATISTICAL ANALYSIS:

Following the compilation of data of the different case records, explanatory analysis was made.

RESULTS AND OBSERVATION:

In this study 24 patients could be enrolled out of which 22 (91.66%) were male and 2 (8.33%) were female. Average age of the patients was 54±11.72 years. Youngest patient was of 31 yrs and oldest was 80 yrs. Maximum number of patients of myocardial infarction was in the age group of 5th and 6th decades (29.16%). Table 1 shows the age and sex distribution of the STEMI patients.

Table 1 : Age and Sex distribution of STEMI patients.

Age group(in years)	Male	Female	Total
31-40	03	00	03
41-50	06	01	07
51-60	06	01	07
61-70	05	00	05
71-80	02	00	02
Total	22	02	24

Out of 24 patients 13 (54.16%) were hypertensive, 1 (29.1%) were diabetic, 1 patient (4.16%) had family history of coronary artery disease, 14 (58.3) including 1 female were smoker and 3 (12.5%) were alcoholic. If the lipid profile is considered, 23 (95.83%) patients had serum cholesterol > 150 mg %, 22 (91.66) had serum LDL> 100mg% and 17 patients (70.83%) had serum HDL < 40mg%.

Out of 24 STEMI patients 14(58.33%) had anterior wall myocardial infarction, 8 patients(33.33%) had inferior wall myocardial infarction and 2 patients(8.33%) had both anterior and inferior wall involvement. Out of 14 anterior wall STEMI patients, 2 (14.28%) patients had extensive anterior wall MI, 4(28.57) had anterolateral wall MI, 3 (21.42%) had anteroseptal wall MI and other 5 (35.71%) had anterior wall MI.

The average duration of chest pain the patients presented with was around 3 hrs, precisely 176.66 ±80.33 mins. The average time taken to initiate the thrombolytic therapy i.e door to needle time was 229.92± 13.96 mins, approximately 4hrs. The average time taken for affective thrombolysis which was indicated by 50 % reduction of ST segment elevation or appearance of ill sustained VT was approximately 1½ hrs, precisely 95.45± 28.07 mins.

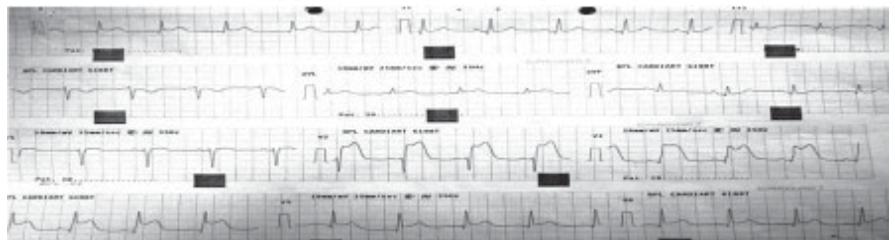


Fig 1. Acute anterior wall STEMI before thrombolysis.



Fig 2. 30 mins after thrombolysis.



Fig 3. 60 mins after thrombolysis.



Fig 4. 90 mins after thrombolysis.

Two patients (8.33%) out of 24 expired. One patient had cardiogenic shock on presentation and could not be revived and the other one expired due to hemorrhagic cerebrovascular accident, probably due to complication of the drug. One patient had to be transferred to higher centre due to failed thrombolysis. 21(87.5%) other patients recovered well without any complication and discharged. Two patients (8.33%) had bleeding complication, out of these one had hemorrhagic CVA who expired and the other one had minor gum bleeding which recovered spontaneously.

DISCUSSION:

In this study the mean age of the patients is 54 ± 11.72 years, which is similar to the landmark trials conducted on reteplase eg. RAPID-1(57yrs) and RAPID-2(58yrs)⁶. One Indian study also had 58 ± 12.67 years of average age⁷. Another study, where reteplase was used as a prehospital administration, also had average age of 60yrs⁸. Male patients are predominantly more (91.60%) in our study as was found in studies by Shah K et al⁷ and Morrow D et al⁸. Our study had 14 patients (58.33%) of anterior wall MI which is slightly higher than the RAPID-1 trial

(50%) where the 10+10 iu of reteplase was used in a bolus dose⁶. RAPID-2 study had 39% of anterior wall MI⁶.

The average time taken by the patients to attend our Hospital following symptom onset was 176.66 ± 80.33 mins (approximately 3hrs) which much lower than the average time mentioned in CREATE registry of India (360 mins)³. The average time to initiate the thrombolysis following symptom onset was 229.92 ± 13.96 mins (approximately 4 hrs) which was longer than both RAPID-1 (3.0 ± 1.4 hrs) and RAPID-2 (3.2hrs)⁶. The study conducted by Morrow D et al⁸ the door to needle time for prehospitalisation group was much low, only 31 mins and also for hospitalized group ie. 63 mins.

The effectiveness of reteplase as thrombolytic as evidenced by TIMI-3 score by angiography at 60 and 90 mins was 63% and 60% in RAPID-1 and

RAPID-2⁶ which was not possible to confirm in this study as this facility is not available in our institution. Still, from the serial ECGs taken at different intervals following thrombolysis showed that the time required for affective thrombolysis following reteplase infusion was 95.45 ± 28.07 mins.

Overall bleeding episode was 8.33% in our study which is almost similar to the study conducted by Shah K et al⁷ ie, 7.5%. Though INJECT trial showed higher incidence of overall bleeding episodes-(15%)⁹. Major bleeding episode in our study was found in 4.16% cases which agrees with INJECT(4.6%)⁹ and RAPID-2(5.3%)⁶. RAPID-1 showed higher incidence of major bleeding 13.6%⁶. Minor insignificant bleeding episodes was also very less in our study 4.16%. Though stroke was found very less in number in different studies, eg. In GUSTO III- 1.64%⁽¹⁰⁾, RAPID-1-0%, RAPID-2-1.8%⁶, INJECT trial⁹ showed small insignificant in hospital stroke 1.23% with haemorrhagic stroke 0.77%, in our study we had 4.16% stroke in our study. This may be attributed to less number of patients in our study.

Finally, the 30-35 day mortality rate in this present study was found to be 8.33%, which agrees with GUSTO-

III trial¹⁰ and the study conducted by Shah K et al⁷ where the mortality rate was little less-7.47% and 6.25% respectively. In RAPID-1 and RAPID-2 trials⁶ had low mortality rate-1.9% and 4.1% respectively. This significant difference in mortality rate may be attributed to the longer time taken to initiate the thrombolysis in our study (approximately 4hrs vs 3±1.4hrs in RAPID-1 & 3.2hrs in RAPID-2) as it is said that time in muscle in MI.

CONCLUSION:

Out of the two methods of reperfusion therapy namely primary percutaneous coronary intervention (primary PCI) and thrombolysis, PCI had proved to be superior beyond doubt. But, PCI facility is till now available mostly in urban areas and in few centers all over the country and the world. The affordability is also an obstacle to avail the facility of PCI. Different studies have proved that in the first hour of acute STEMI, i/v thrombolysis results can be at par with PCI. The studies conducted till now all over the world have proved that i/v reteplase can be an ideal thrombolytic agent considering in efficacy, side effects and easy process to administer. We with all our available resources have tried to evaluate the efficacy of Reteplase as a thrombolytic agent in this institution which is situated in the furthest and remotest corner of the country and found that it may be used as an alternative to primary PCI, till this facility comes up in near future.

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Neurological Spectrum of Wilson's Disease in North-East India : A Hospital Based Observational Study

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Abstract

Background : Wilson's disease (WD) can have predominant neurological presentation. Due to challenges in recognition and classification of its various complex neurological features, misdiagnosis is common leading to delay of in arriving at correct diagnosis of a treatable disorder. **Objective:** To study the neurologic manifestations of WD in patients of North-East India. **Methods:** In an observational study from August 2010 to September 2012 in the Neurology department of a tertiary care hospital, WD was diagnosed by the typical neuropsychiatric manifestations, low serum ceruloplasmin, neuroimaging and the presence of Kayser–Fleischer ring in the cornea. Patients were evaluated by detailed history and clinical examination. **Results:** 15 patients (males 13, females 2) were diagnosed with WD during the study period. Neurological manifestations included tremor, dystonia and dysarthria as the most common signs followed by bradykinesia, choreoathetosis, cerebellar dysfunction, gait abnormalities, seizures, drooling of saliva, proximal weakness and cognitive dysfunction. The mean age of onset of neurological presentation was 18.3 years. **Conclusion:** Patients of Neurological WD presented in the 2nd or 3rd decade of life with predominant tremor, dystonia and dysarthria in North-East India.

KEY WORDS: Wilson's Disease, tremor, dystonia, dysarthria

INTRODUCTION :

Wilson's disease (WD) is an inherited autosomal recessive disorder characterized by abnormal deposition of copper in the basal ganglia, eyes, liver and other tissues. It is caused by mutations in the gene coding for ATPase copper transporting α -polypeptide (ATP7B), which is located on chromosome 13 and is expressed predominantly in the liver.¹ It was first described by Dr Samuel Alexander Kinnier Wilson in 1912.² WD can have neuropsychiatric, hepatic, renal, osseomuscular, hematological, cardiac and dermatological manifestations. Herein, we aim to study the neurological manifestations of WD in patients of North-East India.

METHODS :

We carried out an observational study on patients of WD in the Neurology Department of Gauhati Medical

College, Guwahati, from August 2010 to September 2012. WD was diagnosed by the typical neuropsychiatric manifestations, low serum ceruloplasmin, neuroimaging and the presence of Kayser–Fleischer (KF) ring in cornea. Evaluation of patients included history, thorough neurologic examination and slit lamp examination of the eyes. Laboratory investigations included complete blood count, liver function tests, renal function tests, serum electrolytes, blood sugar, TSH, urinalysis and serum ceruloplasmin in all patients. Serum copper and 24-hours urine copper were done in selected patients. All patients underwent magnetic resonance imaging (MRI) of the brain and ultrasound abdomen. Electroencephalography (EEG) was done in patients with seizures. The patients were treated with D-penicillamine or trientine and zinc.

RESULTS :

During the study period, 15 patients were diagnosed with WD. The mean age of onset was 18.33 years (range 11 to 26 years). Majority of them were males (n = 13, 86.7%). Neurological manifestations included tremor, dystonia, dysarthria, bradykinesia, choreoathetosis, cerebellar dysfunction, gait abnormalities, seizures, drooling of saliva and cognitive dysfunction. Tremor was the most

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common neurological manifestation (n = 15, 100.0%). Patients more commonly had bilateral (n = 12, 80.0%) than unilateral (n = 3, 20.0%) tremor. Majority of them had coarse (n = 13, 86.7%) postural tremor, while few (n = 2, 13.3%) had fine rest tremor. The classical wing beating tremor described in Wilson's disease was observed in only one patient. Most of the patients had dystonia (n = 13, 86.7%), which was either generalized (n = 10, 66.7%), segmental (n = 2, 13.3%) or focal (n = 1, 6.7%). Other salient features included psychosis (n = 2, 13.3%) and proximal weakness (n = 2, 13.3%). KF ring was present in all the patients. Siblings of 3 (20%) patients had history suggestive of neurological Wilson's disease. Hepatic dysfunction (jaundice) was present in 6 (40%) patients. The results are summarized in Table 1.

Table 1. Profile of 15 consecutive patients of Wilson's Disease

Characteristic	Value
Age of onset in years, mean (range)	18.33 (11 – 26)
Males, n (%)	13 (86.7)
Clinical features	
Tremor, n (%)	15 (100.0)
Unilateral, n (%)	12 (80.0)
Bilateral, n (%)	3 (20.0)
Postural, n (%)	13 (86.7)
Rest, n (%)	2 (13.3)
Dystonia, n (%)	13 (86.7)
Generalized, n (%)	10 (66.7)
Segmental, n (%)	2 (13.3)
Focal, n (%)	1 (6.7)
Bradykinesia, n (%)	9 (60.0)
Choreoathetosis, n (%)	3 (20.0)
Cerebellar dysfunction, n (%)	4 (26.7)
Gait abnormality, n (%)	10 (66.7)
Dysarthria, n (%)	13 (86.7)
Drooling of saliva, n (%)	6 (40.0)
Seizures, n (%)	2 (13.3)
Cognitive dysfunction, n (%)	3 (20.0)
Psychosis, n (%)	2 (13.3)
Proximal weakness, n (%)	2 (13.3)
MRI brain (T2-weighted images)	
Basal ganglia hyperintensities, n (%)	15 (100.0)
Thalamus hyperintensities, n (%)	10 (66.7)
Brainstem hyperintensities, n (%)	4 (26.7)
Cerebral atrophy, n (%)	4 (26.7)
Cerebellar atrophy, n (%)	4 (26.7)
Positive family history, n (%)	3 (20.0)
Hepatic dysfunction, n (%)	6 (40.0)

Serum ceruloplasmin levels were low (<0.2 g/L) in all our patients. Serum copper levels were done in 2 patients and were found to be below 75 mg /dL in both.

24-hours urinary copper excretion was done in 2 patients and levels were above 100 µg in both. All of the patients had abnormalities in MRI brain in the form of hyperintensities in basal ganglia (n = 15, 100%), brainstem (n = 10, 66.7%) and thalamus (n = 4, 26.7%) on T₂-weighted images and cerebral (n = 4, 26.7%) and cerebellar atrophy (n = 4, 26.7%). The characteristic 'face of a giant panda' sign was seen in one patient.

DISCUSSION :

Neurological presentation of WD is seen in 40-50% patients with mean age of onset 19 years (range, 6 – 72 years). Hepatic manifestations usually occur a decade earlier and psychiatric features develop later. The neurological features may be categorized predominantly into one of the following: dysarthric, dystonic, tremulous, pseudosclerotic (tremor with or without dysarthria), parkinsonian and ataxic. Initially, only one symptom may be present (often unilaterally), but as the disease progresses, complex combinations of neurologic signs and symptoms may develop leading to difficulty in classification. Tremor is the most frequent neurological symptom, occurring in almost 80% of patients. Tremor can be resting, intentional and/or postural, often with a "wing-beating" character. Parkinsonian features (40%) include hypomimia, drooling, micrographia, and bradykinesia. About 10-30% have dystonic presentation, either as focal (risus sardonius, orofacial dystonia, hand dystonia [Figure 1], tongue dystonia), segmental (trunk dystonia) or generalized dystonia. Dystonia of the facial and jaw muscles can produce a stiff face with a gaping mouth known as a 'vacuous smile'. Dysarthria, seen in majority, may be classified as d y s t o n i c ,





Figure 2

cerebellar, parkinsonian or remain unclassified. Other uncommon manifestations include autonomic involvement (hypersalivation, orthostatic hypotension), cerebellar ataxia, chorea, ballism, myoclonus, tonic-clonic seizures (generalized or focal) and pyramidal signs. Patients can occasionally show painful proximal weakness suggestive of myopathy.^{3,4} About one-third of patients experience psychiatric disturbances in the form of attention deficit hyperactivity disorder, impulsivity, paranoid psychosis, obsessive behavior, depression, suicidal tendencies or bizarre behavior.⁵ Ocular signs include KF ring [Figure 2], sunflower cataract and abnormalities in ocular movements like slow horizontal saccades, upward gaze restriction, impaired convergence and eyelid apraxia.⁶

Many Indian data are available on WD. In National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, about 15-20 new cases of WD are registered annually. The neurological manifestations of WD in a cohort of 282 patients were parkinsonism (62.3%), dystonia (35.4%), cerebellar signs (28%), pyramidal signs (16%), chorea (9%), myoclonus (3.4%), athetosis (2.2%) and behavioral abnormalities (16%). WD was more common in male (male: female ratio = 2.28: 1). Mean age of onset was 15.9 years. All neurological patients had KF rings.⁷ In another study from Eastern India (n= 49), dystonia (96%) was more common, followed by dysarthria (80%), cognitive decline (71%), tremors (47%) and bradykinesia (45%).⁸ Musculoskeletal form of Wilson's disease is reported from Indian studies.⁹ The reported frequency of KF ring in various Indian case series range from 86.6 to 97.1%.¹⁰

MRI is the preferred neuroimaging modality for WD. In T₁-weighted images, generalized brain atrophy is seen in three-quarters of cases, and hypointensities in the basal ganglia in two-third of cases. In T₂-weighted images, one-third of cases demonstrate hyperintensities in the basal ganglia, white matter, thalamus or brainstem. These abnormalities are caused by neuronal loss, gliosis, degeneration of fibers, and vacuolization associated with increased water content in the brain. Signal abnormalities vary according to the stage of the disease, and can be reversible with therapy in the early stages.¹¹

A two tier global assessment scale has been developed for monitoring progression and for therapeutic interventions in patients with WD. Tier 1 scores the global disability in four domains, namely liver, cognition and behavior, motor, and osseomuscular. Tier 2 is multidimensional scale for a fine grained evaluation of the neurological dysfunction.¹² Treatment of neurological WD involves symptomatic therapy and copper chelation with D-penicillamine, trientine and ammonium tetrathiomolybdate (not available commercially). Zinc may be used in presymptomatic patients and during the maintenance phase of treatment of symptomatic patients. However, zinc does not chelate copper and may not be adequate as monotherapy in the initial intensive phase of treatment in symptomatic patients. Indian literature is not clear about the role of zinc as a monotherapy as there are reports of deterioration following zinc therapy alone. The combination of zinc with chelators presents significant dosing issues because both the chelators can potentially chelate zinc, reducing the bioavailability of the chelators as well as that of zinc. Chelation induced neurological worsening usually manifests with abrupt clinical deterioration over days or weeks. It is alleviated with continuation of therapy or with down-titration of the dosages. The patients intolerant to medical treatment may be offered liver transplantation.^{13,14} Most of the patients in our study showed improvement with penicillamine and zinc. Two patients who showed worsening were shifted to trientine or zinc monotherapy.

Although our study includes small number of patients, we hope to increase the awareness on neurological manifestations of WD in North-East India and highlight the importance of careful ophthalmologic examination (under slit lamp) in any patient with movement disorder. Misdiagnosis at initial evaluation is common (62.5%),

leading to a mean delay of two years in arriving at correct diagnosis of a treatable disorder.¹⁵

CONCLUSION :

WD should be suspected in any young patient presenting with movement disorders. In North-East India, patients usually present in the second and third decade of life with tremor, dystonia, dysarthria and parkinsonism but cerebellar ataxia, seizures and cognitive dysfunction may also be seen. Early recognition of neurological WD is important because the disease is potentially treatable.

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Anaerobic Pleuro – Pulmonary Infections : Is Routine Culture Necessary?

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Abstract

Background: Anaerobes play a major role in pleuropulmonary infections. Obligate anaerobes are the predominant constituents of normal oropharyngeal flora and produce pleuropulmonary infection in patients who are prone to aspirate. Predisposing conditions include prominent dental disease, chronic upper respiratory tract infections and reduced consciousness. **Aims:** To isolate both aerobic and obligate anaerobic bacteria implicated for causing pleuro – pulmonary infections and to evaluate the necessity of routine anaerobic culture for such infection. **Settings and Designs:** A prospective study was conducted over a period of one year. **Methods:** Specimens of pleural fluid, empyema fluid, and aspirates from lung abscess, collected through transthoracic route and blood were collected from 55 patients, clinically suspected to have pleuro-pulmonary infections. Specimens were processed for isolation of both aerobes / facultative anaerobes and obligate anaerobes using standard microbiological techniques. **Results and Observation:** Out of the 55 cases included in the study, 18 (32.7%) cases showed growth of aerobic organisms while 2 (3.63%) cases showed the growth of anaerobic organisms, the rest being culture negative. From the culture positive cases, the most commonly isolated aerobe was *Klebsiella pneumoniae* (36.84%), followed by *Staphylococcus aureus* (21.05%), *Pseudomonas* spp. (15.78%), *Streptococcus pneumoniae* (10.52%), *Escherichia coli* (5.26%) and *Proteus vulgaris* (5.26%). *Prevotella* spp. was the only anaerobe isolated from 10.52% of the culture positive cases. Blood cultures revealed no growth of any organisms. **Conclusion:** To obtain proper clinical specimens for anaerobic culture is very difficult and also the process of culturing these organisms is very expensive and time consuming. Suspected anaerobic infections can be treated with empirical antibiotics guided by published studies. Therefore routine culture and susceptibility testing for such infection is rarely warranted.

KEY WORDS: anaerobes, pleuro – pulmonary infections

INTRODUCTION :

Anaerobic bacteria have been implicated in aspiration pneumonia and its sequelae, including lung abscess, necrotizing pneumonia and empyema since the early 1900s¹. Obligate anaerobes are the predominant constituents of normal oropharyngeal flora and produce pleuro – pulmonary infection in patients who are prone to aspirate². Predisposing conditions include prominent dental diseases, chronic upper respiratory tract infections and reduced consciousness³.

It has also been found that the aetiology of pleuro-pulmonary infections depends on the geographic region,

patient's age and advances in the diagnosis and treatment of the underlying cause^{4,5}.

Anaerobic bacteria play a relatively well confirmed role in selected types of pulmonary infections that are uncommon but distinctive, with common clinical features that include indolent course, putrid discharge and response to antibiotics directed at anaerobes including clindamycin or β -lactam – β -lactamase inhibitors that are favoured for most cases of lung abscess¹.

The clues to the subset that do involve anaerobes include probable aspiration as evidenced by dysphagia (inability to drink water rapidly) or reduced consciousness along with infection in a dependent pulmonary segment with aspiration in the recumbent position or basilar segments with aspiration in the upright position; putrid discharge (sputum, empyema fluid), diagnostic of anaerobes; indolent course (nonspecific); necrosis of tissue with necrotizing pneumonia, lung abscess or empyema with a bronchopleural fistula¹.

Most cases of pneumonia probably do not involve

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anaerobic bacteria. In addition, the antimicrobials that are commonly used for community acquired pneumonia and other common lung infections like β -lactams, macrolides and flouroquinolones have sufficient activity versus upper airway anaerobes¹.

Obtaining material from these patients for culture from the site of infection that is uncontaminated by normal flora is problematic. In vitro cultivation of obligate anaerobes requires rigorous anaerobic techniques and susceptibility testing of obligate anaerobes is not standardized in many clinical microbiology laboratories. Few clinical trials of drugs have been done in patients with laboratory documented or putative anaerobic pulmonary infection. For these reasons the diagnosis and therapy of anaerobic pulmonary infection are frequently empirical and guided by published studies of in – vitro activity against collected clinical isolates¹.

Considering the above, the present work was undertaken to isolate and identify the bacterial agents causing pleuro - pulmonary infections and to evaluate whether it is actually required to carry out anaerobic cultures on a routine basis in order to manage such infections.

MATERIALS AND METHODS :

The study involved 55 patients suspected to have anaerobic pleuro – pulmonary infections and was done in a tertiary care hospital in Assam, India.

Two specimens of pleural fluid, empyema fluid or aspirates from lung abscess were taken from each patient who had the predisposing factors that might lead to anaerobic pleuro – pulmonary infections. The specimens were collected either transthoracically or intraoperatively. Gram stains of all the specimens were made and processed following the standard microbiological techniques for isolation and identification of both aerobic and anaerobic organisms^{6,7}.

For isolation of anaerobic organisms, ready to use Thioglycollate broth from Hi Media Laboratories Pvt. Ltd. Mumbai were used as a media for collection and transport of the specimens. The specimens were collectcted in sterile syringes and inoculated immediately to the pre reduced thioglycollate broth avoiding introduction of any air. Then the broth were incubated anaerobically for 48 hours at 37⁰C. Then the broth was subcultured on anaerobic blood agar media and incubated in an anaerobic jar at 37⁰ C for

48 hours. Anaerobiasis was achieved by anaerobic gas packs commercially available from Hi Media Laboratories Pvt. Ltd. Mumbai. The organisms isolated anaerobically are further subcultured on blood agar, MacConkey agar and anaerobic blood agar media and incubated in aerobic and anaerobic conditions respectively to deduce whether the isolate is facultative or obligate anaerobe. Obligate anaerobes showed no growth in plates incubated aerobically and facultative anaerobes were found to be grown in both aerobic and anaerobic conditions. Identification of anaerobic organisms was done manually according to standard guidelines.

For isolation of aerobic organisms, the specimens were collected in a sterile tube. Gram stains were prepared from all the specimens and were inoculated on blood agar and MacConkey agar media. Isolated organisms were identified manually according to the standard guidelines⁷. Two specimens of blood were taken from all the patients and were processed for isolation of aerobic, facultative anaerobic and obligate anaerobic bacteria.

Isolates of *Staphylococcus aureus* were screened for MRSA using standard guidelines.

All the isolated bacteria were tested against different antimicrobial agents by standard disc diffusion method (Kirby Bauer Technique).

RESULTS :

Out of the 55 cases included in the study, 18 (32.7%) cases showed growth of aerobic organisms while 2 (3.63%) cases showed the growth of anaerobic organisms, the rest being culture negative. (Table 1)

Table 1: Culture results of the specimens of the 55 cases included in the study

TYPE OF ISOLATES	NO.	PERCENTAGE
Only aerobes	17	89.48%
Only anaerobes	1	5.26%
Both aerobes and anaerobes	1	5.26%
TOTAL	19	100%

Of the four isolates of *Staphylococcus aureus*, two were found to be MRSA.

Of the enterobacteriaceae group, the organisms showed maximum sensitivity to Imipenem (100%), followed by Cefotaxime (77.77%), Piperacillin – Tazobactam and Gentamicin (66.66%), Ciprofloxacin (55.55%), Cefepime (33.33%) and Cefuroxime (22.22%). All the organisms showed resistance to Ampicillin.

Table 2 : Various bacterial isolates of the culture positive cases

Aerobic isolates	
1. Gram negative bacilli	No. (%)
<i>Klebsiella spp</i>	7 (35%)
<i>Pseudomonas spp</i>	3 (15%)
<i>Escherichia coli</i>	1 (5%)
<i>Proteus vulgaris</i>	1 (5%)
2. Gram Positive cocci	No. (%)
<i>Staphylococcus aureus</i>	4 (20%)
<i>Streptococcus pneumoniae</i>	2 (10%)
Total aerobic isolates	18 (90%)
Anaerobic isolates	
Gram negative bacilli	
<i>Prevotella spp.</i>	2 (10%)
Total no. of isolates	20 (100%)

The isolated *Pseudomonas* spp showed maximum (100%) sensitivity to Imipenem and Polymyxin B, followed by Amikacin, Tobramycin and Ceftazidime (66.66% each) while Piperacillin – Tazobactam and Ciprofloxacin shows 33.33% sensitivity. None of the *Pseudomonas* isolate was sensitive to Aztreonam.

The Staphylococcal isolates showed maximum (100%) sensitivity to vancomycin and Linezolid, followed by Amoxyclav, Erythromycin and Doxycyclin (50% each) while Gentamicin and Ciprofloxacin shows 25% sensitivity. All isolates were resistant to Penicillin.

Both the isolates of *Streptococcus pneumoniae* were sensitive to Penicillin, Gentamicin, Vancomycin and Linezolid, while one isolate was found to be sensitive to Amoxyclave.

The two isolates of *Prevotella* spp. were sensitive Clindamycin, Piperacillin-Tazobactam, Cefotaxime and Imipenem while only one isolate was found to be sensitive to cefuroxime and Ciprofloxacin. Both the isolates were resistant to Metronidazole and Ceftriaxone. Blood culture was done from all the 55 cases of included in the study, but none of the cases revealed growth of any organisms.

DISCUSSION :

Out of the 55 cases included in the study, 18 (32.7%) cases showed growth of aerobic organisms while 2 (3.63%) cases showed the growth of anaerobic organisms, the rest being culture negative. Similarly S. Tareen et al¹ found 26% cases to be culture positive and could not recover any anaerobic organism, K. Wanjari⁸ also found only 11.16% of the cases to be culture positive and could not recover any anaerobic organism.

But in comparison to some other studies,^{9, 10, 11, 12, 13}

the present study reveals lower isolation rate of anaerobic organisms. This might be due to administration of empirical antibiotics that are commonly instituted in such patients to stabilize or probably there may not be common involvement of anaerobic bacteria as the etiological agent in such infections in this region of the world as involvement of anaerobes may have a geographical distribution as reported by some studies^{4, 5}.

In our study, it was found that amongst the culture positive cases, the most commonly isolated aerobic organism was *Klebsiella pneumoniae* (36.84%), followed by *Staphylococcus aureus* (21.05%), *Pseudomonas* spp. (15.78%), *Streptococcus pneumoniae* (10.52%) and *Escherichia coli* (5.26%) and *Proteus vulgaris* (5.26%). *Prevotella* spp. was the only anaerobic organism isolated from 10.52% of the cases. Such findings were also reported by K. Y. Chen et al⁹ and Jiun – Ling Wang et al¹⁴ who reported *Klebsiella pneumoniae* to be the most commonly isolated organism. D. Panigrahi et al¹⁵ also found *Klebsiella pneumoniae* as one of the predominant aerobic pathogen and *Prevotella* spp as the commonest anaerobic isolate.

Blood culture was done from all the 55 cases included in the study, but none of the cases revealed growth of any organism. Such findings were also reported by I. Yaacob and Z. Ariffin¹⁶ who failed to grow any organism from blood culture in 7 out of 13 patients with empyema and could recover *Streptococcus viridans* from only one case out of 9 cases of lung abscess. But J.L. Wang et al¹⁴ reported 18% positive blood cultures in patients with lung abscess.

The negative result for blood cultures in the present study may be attributed due to early administration of antibiotics; moreover the sensitivity of blood cultures can be increased by proper timing of specimen collection and increasing the number of specimens.

Few of the aerobic bacterial isolates were found to be resistant to third and fourth generation Cephalosporins. However all the isolates were sensitive to Carbapenems. Both the anaerobic isolates though sensitive to most of the antibiotics were resistant to metronidazole.

According to the published guidelines, for community acquired infections, the recommended antibiotics include intravenous amoxicillin – clavulanic acid or a combination of a second generation cephalosporin (e.g. cefuroxime) or clindamycin if the patient is allergic to penicillin and metronidazole¹⁷.

Patients with nosocomial infections need adequate Gram negative coverage as Gram negative organisms are more common in nosocomial infections. For these cases coverage should include at least a carbapenem or antipseudomonal penicillin (e.g. piperacillin – tazobactam) or third or fourth generation cephalosporins (e.g. ceftazidime, cefepime) with metronidazole. If there is a strong suspicion of MRSA coinfection, vancomycin or linezolid can be added. Aminoglycosides should be avoided as these may be inactivated at low pleural fluid pH and are ineffective against anaerobes¹⁷.

CONCLUSION :

Microorganisms that constitute the normal oropharyngeal flora may gain access to the deeper lung tissues in individuals prone to aspirate. Oropharyngeal secretions are loaded with both aerobic and anaerobic organisms in high concentrations, therefore in an already diseased lung or in generalised immunosuppression, these organisms might overcome the defence mechanism and establish infection.

Different studies have reported that anaerobic organisms are causal factors of various types of pleuro – pulmonary infections. In the current study also two anaerobic organisms were isolated.

But routine culture of anaerobic organisms is a time consuming and expensive task. Collection of appropriate samples and their transport to the laboratory is also very meticulous and must be done properly for successful isolation of anaerobes. Moreover susceptibility testing of anaerobic organisms is not standardized. Considering the above facts it is very difficult to carry out anaerobic culture in a routine basis.

The recommended treatment for anaerobic pleuro – pulmonary infections surgical intervention and antibiotic administration as early as possible. As culture and antibiotic susceptibility of anaerobes takes a lot of time, it always becomes necessary to start empirical antibiotic administration in order to contain such infection.

As recommended by many other published reports^{2,18} authors of this study would also like to conclude that routine culture and susceptibility testing of anaerobic organisms is not warranted. But studies on anaerobic isolates of pleura – pulmonary infection should be carried out so as to keep track on the changing trend of anaerobic

isolates as causative agents of such infections and their susceptibility pattern.

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A study of health related quality of life in COPD patients in relation to severity of disease

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ABSTRACT:

Patients with COPD have impaired health related quality of life (HRQOL); only a part of this is reflected in clinical and demographic measures. The physiological variable and disease severity has an impact on the Quality of Life (QOL) of this group of patients. This study investigated the factors influencing the quality of life of 200, COPD indoor and outdoor patients, in Assam. COPD patients who had $FEV_1/FVC < 70\%$ (no reversibility) post bronchodilator were included in the study. Spirometry and MMRC scale for dyspnea were evaluated for all the cases, 6-minute walk test (MWT) was performed for the selected cases who could perform it. They underwent St. George's Respiratory Questionnaire (SGRQ) to measure HRQOL. Patients with COPD showed significantly reduced HRQOL as measured by SGRQ. The QOL was worsening along with worsening physiological measurements and disease severity.

BACKGROUND :

COPD is the 4th leading cause of death in the world¹ and further increased in its prevalence and mortality can be predicted in coming decades.² With the increasing prevalence of smoking in developing countries, it is projected that COPD related mortality morbidity will dramatically impact Asian & African Countries.³ According to crude estimates, 30 million people suffer with COPD in India, and these numbers are only going to increase in the forth coming years. According to a report published by the national centre for Macroeconomics and Health, the estimated economic loss due to COPD in India is Rs. 35,000 Cores.⁴ The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2001 defined Chronic Obstructive Pulmonary Disease as a disease state characterised by chronic airflow obstruction that is not fully reversible. This airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious practices or gases.⁵ The person who lives in smoky surroundings either because of fire or tobacco is more likely to develop COPD. Impaired lung function in

COPD leads to dyspnea and impaired exercise tolerance; this in turn influences patient's quality of life (QOL).⁶ HRQOL defined as the degree to which a patient's health status affects his or her self determined evaluation of satisfaction or QOL as an important prognostic factor in COPD patients.⁷

HRQOL scores have been useful for the health care professionals in addition to the physiological, clinical measurements to evaluate health status, the impact of disease on patient wellbeing. The HRQOL Scores were helpful to develop interventions directed toward improving their care. There are no published literatures regarding factors affecting the QOL among COPD patients in Assam. The present study aims to investigate the relationship of demographic variables, disease severity and physiological parameters with QOL in COPD Patients.

MATERIALS AND METHODS :

This descriptive study was conducted at Gauhati Medical College and Hospital (GMC&H), Guwahati, Assam. The total 21,750 patients visited in the respiratory outpatient department during the year 2011 and 2012. Out of them 566 patients were diagnosed as COPD cases. The study population comprised of adult clinically stable COPD patients above 40 years, who had visited outpatient and admitted in the respiratory medicine

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department. 200 cases were taken randomly on alternate day basis to cover all the visiting physicians' cases. Patients with FEV₁/FVC ratio <70% predicted post bronchodilator and FEV₁ reversibility <12% were included in the present study. Subjects who had history of Chronic Lung Disease such as bronchiectasis, asthma, interstitial lung disease, any malignant condition, obstructive sleep apnoea syndrome and cardiac diseases were excluded from the study.

Detail explanation was given to the subjects and consent had been taken prior to the data collection. Each study participant had undergone spirometric measurements, performed by trained professionals according to the American Thoracic Society Guidelines.⁸ Disease severity was classified according to the GOLD criteria.⁹ The 6-MWT was performed in a 25 meter long corridor according to the American Thoracic Society Guidelines.¹⁰ The severity of dyspnea was measured by the modified Medical Research Council (MMRC) dyspnea scale.¹¹ HRQOL was measured by SGRQ-C, which is a standardised, self administered disease specific questionnaire. SGRQ-C consist of 40 items, divided into three sub-scale Symptoms (7 items), Activity (13 items), Impact (20 items). Scores were expressed as percentage. The total score varies from 0-100, with higher the score indicating worse health status.¹² The tool was translated to the mother tongue (Assamese) of the participants, for their better understanding.

STATISTICAL ANALYSIS :

Results were reported as mean ± SD. The relationship between HRQOL scores and continuous variable were assessed using Pearson correlation coefficient (r). p-value <0.05 was considered statistically significant.

Majority of the subjects 79(39.5%) were in the age group of 61-70 years. The study sample was dominated by the male (84%) gender. However it had been noticed that female were suffered the more severe disease state at an early age. Among male subjects 64 of them were ex-smoker and 85 were current-smoker. Female subjects were exposed to biomass fuel (fire wood) for cooking food more than 10 years.

Among the 200 subjects nobody was in the mild classification. Majority of the subjects 92(46%) fell in

Table 1 : Distribution of COPD subjects characteristics according to demographic variables

		No.	Percentage
Age in years	41-50	24	12.0
	51-60	42	21.0
	61-70	79	39.5
	>70	55	27.5
Gender	Male	168	84.0
	Female	32	16.0
Education	Illiterate	59	29.5
	Primary school	42	21
	Middle school	18	9.0
	High school	25	12.5
	Secondary	21	10.5
Smoking History	Graduate and above	35	17.5
	Current-Smoker	85	42
	Ex-smoker	64	32
	Non-smoker	25	12.5
	Biomass Fuel	26	13

Table 2 : Distribution of COPD subjects characteristics according to severity of disease:

FEV ₁ predicted %		No.	Percentage
GOLD Classification	GOLD1: Mild ≥80	0	0
	GOLD2: Moderate 50-79	92	46
	GOLD3: Severe 30-49	61	30.5
	GOLD4: Very severe <30	47	23.5

Table 3 : Descriptive statistics according to the degree of Quality of Life

HRQOL	Symptom		Activity		Impact		Total-QOL	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Poor	29.7	8.1	18.8	2.0	35.1	.4	19.6	1.9
Very poor	62.7	13.2	22.6	2.7	35.4	.4	27.5	2.9
Worst	94.8	3.6	26.2	1.0	35.9	.6	35.2	.9

the moderate classification. From the subjects 61(30.5%) belongs to the severe disease state of COPD. There were 47(23.5%) subjects in the very severe disease state. The data depicts that majority were at an advanced stage of the disease. It was clear that COPD was not usually diagnosed at an early state.

Degree of Quality of Life influenced the symptom domain. Activity Domain was less influenced by Degree of Quality of Life. Comparing to other two Domain, Impact Domain was slightly influenced by the Degree of Quality of Life.

The Physiologic variables showed weak reverse correlation with Quality of life as well as separate domains of quality of life. FEV₁ showed significant correlations with SGRQ (p<0.01). Likewise, the FEV₁/FVC showed correlations (p<0.01). The impact domain was not influenced by FEV₁/FVC. The 6-MWT, a functional assessment for lung disease, showed significant

Table 4 : Co-relation between Quality of Life (QOL) among COPD patients and Physiologic variables

Physiologic variables	Descriptive statistics			Correlation r value		
	Mean	S. D.	Symptom	Activity	Impact	Total-QOL
FEV ₁	37.05	12.936	-.505(**)	-.514(**)	-.470(**)	-.553(**)
FEV ₁ /FVC	63.07	6.448	-.227(**)	-.227(**)	-.076	-.243(**)
6-MWD	229.29	73.759	-.562(**)	-.507(**)	-.606(**)	-.625(**)

moderate correlation at $p < 0.01$ level. The decline in lung function, worsen the quality of life and decreased exercise performance.

MMRC scale for dyspnea showed positive moderate correlation with quality of life ($p < 0.01$). That means the quality of life was worsening along with worsening impact of dyspnea. Acute exacerbation had moderate positive correlation whereas co-morbid

Table 5 : Co-relation between Quality of Life (QOL) among COPD patients and Severity of disease

Severity of disease	Correlation r value					
	Mean	S.D	Symptom	Activity	Impact	Total
MMRC Scale for dyspnea	2.92	1.096	.627(**)	.478(**)	.679(**)	.696(**)
Acute exacerbation Number	1.42	.805	.478(**)	.365(**)	.414(**)	.499(**)
No. of Co-morbid condition	.74	.746	.199(*)	.248(**)	.200(*)	.233(**)

condition had very weak correlation with quality of life at < 0.01 level. The subjects who were hospitalised with acute exacerbation they had higher impact on their Quality of Life. Among the co-morbid conditions Hypertension, Diabetes mellitus, Acid peptic disorder and prostatic problems were more prevalent. Co-morbid conditions may or may not influence the QOL. From this table it was clear that greater the severity of symptoms, the poorer the QOL.

DISCUSSION :

This study showed that 200 patients from Assam had significantly impaired HRQOL when measured by the generic questionnaire SGRQ. When examining specific domains, all showed significant impairment.¹³The impact domain was almost equally impaired in all three levels of QOL. The spirometry parameters had established a reverse correlation with the SGRQ scores.¹⁴⁻¹⁶ Results showed that there was a relationship between GOLD classifications of COPD by FEV₁ with impaired quality of life.¹⁷All three domains of QOL were similarly impaired by the reduced FEV₁. Normal activity was limited by worsening the lung function. MRC scale for dyspnea showed positive correlation with quality of life. Studies showed that dyspnea perception had a strong

relationship with SGRQ-assessed quality of life.^{18, 19} Acute exacerbation was correlated with HRQOL. The patients with frequent exacerbations had a more rapid decline in lung function, worse quality of life and decreased exercise performance.²⁰ The results of this study confirmed the relationship between 6-MWT distance and quality of life (SGRQ) scores. The exercise intolerance could influence quality of life in COPD patients, as reported previously.²¹ Presence of co morbid condition, lower BMI and greater smoking consumption resulted in poorer quality of life. There was statistically significant relationship between the Quality of Life and educational level of the subjects. The

perception of Quality of Life was improved by the higher educational level of the subjects. The previous studies also reported that older age and greater smoking consumption resulted in poorer quality of life.²²

Limitations of the study were; male subjects were 84.0 % and predominantly severe disease of the study participants as the study was conducted in a hospital setting.

CONCLUSION:

The patients from Assam showed significantly reduced HRQOL as measured by SGRQ. The separate domains namely symptom, activity and impact were impaired. In conclusion, health-related quality of life should be considered in addition to pulmonary function tests to more appropriately assess patients with COPD who were mainly middle aged and were considered as an active part of the society.

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Approach to arthritis

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INTRODUCTION :

About 15-20% of presentations to primary care are musculoskeletal in nature¹. Arthritis is one of the commonest presentations in patients with rheumatological conditions. Inflammation of a joint is termed as arthritis. The common symptoms of arthritis include pain, stiffness, and swelling of the joint. The condition may affect one or several joints throughout the body.

Features of inflammatory arthritis

- 1) Prolonged early morning stiffness (>30 minutes)
- 2) Joint pains improve on activity and worsen at rest
- 3) Joint pains are relieved with non steroidal drugs
- 4) They are associated with the 5 cardinal signs of inflammation (swelling, warmth, pain, erythema and loss of range of movement)
- 5) They are associated with constitutional symptoms (fatigue, loss of appetite, loss of weight, low-grade fever or night sweats)
- 6) They are characterised by the presence of
 - High ESR, CRP and platelets
 - Low haemoglobin
 - WBC may be high
 - Mild elevation of alkaline phosphatase

	Inflammatory	Non inflammatory
Early morning stiffness minutes	>30 minutes	Usually 10-15
Rest	Better	
Activity	Improvement	Worse
Signs of inflammation	+++	-
Constitutional symptoms	++	-
High CRP, ESR, platelets	++	-

Table 1 : Difference between inflammatory and non inflammatory arthritis

CLASSIFICATION OF ARTHRITIS :

A) Depending on nature of arthritis

- 1) Inflammatory arthritis

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Prototype example- Rheumatoid arthritis, seronegative spondyloarthropathy

- 2) Degenerative arthritis

Prototype example- Osteoarthritis

- 3) Metabolic

Prototype example- gout, CPPD

The inflammatory arthritis can be further subdivided into:

- 1) Rheumatoid arthritis (RA)
- 2) Seronegative spondyloarthropathies
- 3) Juvenile idiopathic arthritis
- 4) Crystal arthropathies
- 5) Haemorrhagic arthritis
- 6) Arthritis associated with infections
- 7) Arthritis associated with Connective tissue diseases, sarcoidosis and vasculitis

The common non inflammatory arthritis can be subdivided into:

- 1) Osteoarthritis (OA)
- 2) Neuropathic arthropathy (Charcot)
- 3) Haemarthroses
- 4) Ochronosis

B) Depending on the type of onset:

- 1) Acute arthritis
- 2) Chronic arthritis

The common causes of acute arthritis are-

- 1) Septic arthritis
- 2) Crystal arthropathies- Gout/ CPPD
- 3) Haemarthroses
- 4) Reactive arthritis
- 5) Psoriatic arthritis
- 6) Rheumatoid arthritis

The common causes of chronic arthritis are

- 1) Inflammatory arthritis
 - Rheumatoid arthritis
 - Seronegative spondyloarthropathies
 - Crystal arthropathies

Arthritis with CTD
 Arthritis with vasculitis
 Arthritis with sarcoidosis
 Adult onset Still's disease
 Arthritis related to infections (Lyme, viral, bacterial and fungal)

- 2) Non inflammatory
 Osteoarthritis
 Neuropathic arthritis
 Haemarthroses
 Osteonecrosis
 Metabolic

3) Arthritis with tumours

C) Depending on the number of joints involved:

- 1) Monoarthritis
- 2) Oligoarthritis (less than 5)
- 3) Polyarthritis (more than 5)

D) Depending on the site of arthritis

- 1) Peripheral arthritis
- 2) Axial arthritis
- 3) Combination of above

The causes of axial and peripheral involvement with chronic arthritis are

1. Seronegative spondyloarthropathies
2. Juvenile idiopathic arthritis
3. Adult onset Still's disease
4. SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis)
5. Osteoarthritis/ Diffuse idiopathic skeletal hyperostosis
6. Ochronosis

E) Depending on the pattern of arthritis-

1. Symmetric arthritis
2. Asymmetric arthritis
 - a) The common causes of symmetric arthritis are-
 RA
 Psoriatic arthritis- Symmetrical polyarthritis type
 JIA (Polyarticular and systemic types)
 Jaccoud's arthritis (Non erosive deforming arthritis)
 RS3PE- Remitting seronegative symmetric synovitis with pitting edema
 SLE
 Sarcoidosis
 CPPD
 Rheumatic fever

Viral arthritis
 Lyme arthritis
 Haemochromatosis
 Osteoarthritis

- b) The common causes of asymmetric arthritis are-
 Seronegative spondyloarthropathies
 JIA (Oligoarticular)
 Gout
 CPPD
 Septic arthritis and bacterial endocarditis

Inflammatory arthritis

Inflammatory arthritis can be further subdivided depending on the presence of rheumatoid factor:

- 1) Seropositive
 Rheumatoid arthritis
- 2) Seronegative
 Psoriatic arthritis (PsA)
 Reactive arthritis (ReA)
 Ankylosing spondylitis (AS)
 Enteropathic arthritis (En A)
 Juvenile AS
 Undifferentiated

RHEUMATOID ARTHRITIS :

Rheumatoid arthritis is the prototype for inflammatory arthritis. It is a multisystem inflammatory disease that affects about 1% of the population². The peak incidence is in the fourth and fifth decades. The women are 2–4 times more commonly affected than the men³. In India the prevalence of RA was found to be 0.75%⁴. According to the ILAR COPCORD study from Bigwan village the prevalence of RA was 5.5%, A similar study by Mahajan



*Figure 1- Symmetric MCP involvement in RA
 Synovitis affecting MCP joints symmetrically.*

et al found the prevalence for RA was 0.8%^{5,6}.

It is a symmetrical polyarthritis affecting small and large joints (Figure 1). The commonest joints affected are metacarpophalangeal (MCP), proximal interphalangeal (PIP) and metatarsophalangeal joints (MTP) followed by knees and wrists (Figure 2). It can affect the cervical spine especially at C1-C2 level. It is characterised by subcutaneous nodule (Figure 3).

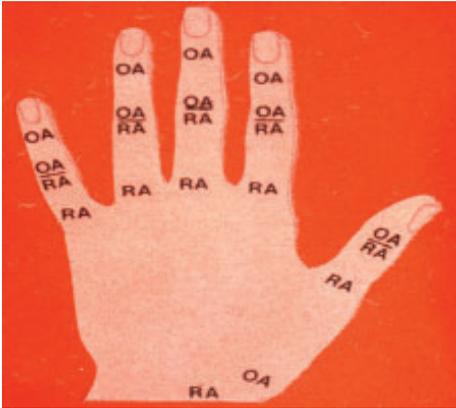


Figure 2- Pattern of joint involvement : RA affects PIP, MCP and wrist whilst OA affects DIP, PIP and 1st carpometacarpal joint.



Figure 3- Rheumatoid nodule : Subcutaneous nodule is usually seen on the extensor aspect of the forearm.



Figure 4- Boutonniere and swan neck deformity associated with RA. Synovitis of MCP joints.

Boutonniere deformity is characterised by no reducible flexion at the PIP joint along with hyperextension of the DIP joint of the finger and swan-neck deformity is characterised by hyperextension at the PIP joint with flexion of the DIP joint.

Multiple deformities are features of RA namely boutonniere deformity (no reducible flexion at the PIP joint along with hyperextension of the distal interphalangeal (DIP) joint of the finger), swan-neck deformity of the finger (hyperextension at the PIP joint with flexion of the DIP joint) (Figure 4), ulnar deviation, subluxation of MCPs and MTPs, square shaped deformity of the thumb, hammer toes and bunion.

Rheumatoid arthritis can be subdivided based on erosions into

- 1) Erosive
- 2) Non erosive

Seronegative spondyloarthropathies

This is an umbrella term for psoriatic arthritis (PsA), reactive arthritis (ReA), ankylosing spondylitis (AS), enteropathic arthritis (En A), juvenile AS and undifferentiated arthritis. Psoriatic arthritis (PsA) affects women and men equally whilst with ankylosing spondylitis, men are affected three times more common than women and most commonly between 20 and 30 years. The prevalence of ankylosing spondylitis in the Caucasian population ranges between 0.15% and 1.8%, and is the most common spondyloarthropathy. The prevalence of psoriatic arthritis ranges from 0.02% to 0.2%, and 6-42% in patients with existing psoriasis⁷. According to the ILAR COPCORD study from Bigwan village the prevalence of ankylosing spondylitis was 0.09%^{5,6}.

Seronegative spondyloarthropathies affect peripheral joints but the most important feature is axial spondyloarthropathy especially sacroiliitis. It is characterised by inflammatory arthropathy (usually large joints, asymmetric), dactylitis and enthesopathy most commonly causing Achilles tendonitis, plantar fasciitis, epicondylitis and costochondritis. Conjunctivitis and acute anterior uveitis are common extra-articular features.

Psoriatic arthritis can present in five different types:

- 1) Oligoarthritis- Usually large joints are affected
- 2) Symmetric (Similar to RA) polyarthritis- Affects small joints of hands, feet, wrist, ankle, knee and elbows
- 3) DIP involvement especially with nail psoriasis
- 4) Axial spondyloarthropathy- Usually asymptomatic asymmetric sacroiliitis usually affects 30% of psoriasis patients.
- 5) Arthritis mutilans- Destructive arthropathy with telescoping feature (Figure 5).



Figure 5- Arthritis mutilans

Destructive arthritis with 'telescoping', X ray hand shows 'pencil in cup' sign.

Degenerative arthritis

Osteoarthritis

Osteoarthritis is a prototype of degenerative arthritis. About 8.5 million people in the UK are affected by osteoarthritis. About 1 in 5 adults aged 50–59 to almost 1 in every 2 adults aged 80+ having painful osteoarthritis in one or both knees^{8,9}. According to the ILAR COPCORD study from Bigwan village the prevalence of osteoarthritis was 5.8%. A similar study by Mahajan et al found the prevalence for OA was 24.9%^{5,6}.

Osteoarthritis can affect any joint in the body. The common joints affected are knees, hips, spine, 1st carpometacarpal joints and MTPs. The symptoms includes pain, minimal stiffness, swelling, locking and loss of mobility. One can find Bouchard's and Heberdon's nodes in nodal osteoarthritis affecting the PIPs and DIPs (Figure 6).



Figure 6-Nodal osteoarthritis

Bouchard's and Heberdon's nodes affecting the proximal and distal interphalangeal joints

METABOLIC ARTHRITIS :

Gout

Gout is a prototype of metabolic arthritis. According to one of the studies the incidence of gout was 2.68 per

1,000 person-years (4.42 in men and 1.32 in women) and increased with age¹⁰. According to the ILAR COPCORD study from Bigwan village the prevalence of gout was 0.1%.⁵

Gout can present as-

- 1) Acute arthritis
- 2) Chronic tophaceous gout

Acute arthritis

It most commonly presents as monoarthritis affecting the first MTP termed as podagra (Figure 7). It commonly affects the first MTP joint, ankle, midfoot and knee. Patients usually complain of excruciate pain so severe that they cannot stand the bed sheet touching the joint. It is associated with inflammatory joint pain with surrounding cellulites. It can be associated with fever. The milder episodes tend to resolve in couple of days.



Figure 7- Gout (Podagra)

Inflamed first metatarsophalangeal joint

Chronic tophaceous gout

Tophi tend to appear in patients affected with gout for more than ten years with few exceptions such as juvenile gout, in presence of myelo/lymphoproliferative diseases or chronic use of diuretics. The common sites are fingers, toes, helix or anti helix of the ear and olecranon bursa (Figure 8). Inflammation is rare except when supervened with acute arthritis.

ASSESSMENT OF ARTHRITIS :

Age and gender of the patients are helpful in diagnosis as the arthritis affect specific age and gender as eluded in the epidemiology section. Past medical history, family history, smoking, alcohol, drug abuse and drug history are helpful especially regarding risk factors. The general



Figure 8- Tophaceous gout
Tophi affecting the metacarpophalangeal and proximal interphalangeal joints

physical examination can reveal pyrexia and tachycardia which could be associated with septic/crystal arthritis. One can find low grade pyrexia with most inflammatory arthritis. Vigilance is needed with septic arthritis as it can seed from other infections in the body, for example- endocarditis, pneumonia etc.

Signs of inflammation (erythema, warm, tenderness and swelling) on joint examination are associated with inflammatory arthritis. Crepitus is a feature of osteoarthritis.

INVESTIGATIONS :

The investigations include blood tests and imaging. Routine blood tests such as full blood count, liver function, kidney function and inflammatory markers are requested to exclude any systemic disease and for monitoring drugs and disease. Rheumatoid factor and anti”cyclic citrullinated peptide can help diagnose RA. HLA B 27 helps with the diagnosis of seronegative spondyloarthropathies. Autoimmune screen (Table 2) with ANA/ENA/dsDNA, complements, cryoglobulin, immunoglobulin, ANCA, ASOT, viral and bacterial screen may be requested depending on the differential diagnosis.

Test	RA	Seronegative spondyloarthropathies	CTD	Vasculitis
RF	+			
Anti CCP	+			
HLA B 27		+		
ANA			+	
ENA- Ro, La,				
Scl 70, Jo, Sm			+	
dsDNA			+	
ANCA				+
Cryoglobulin				+

Table 2- Autoimmune profile

Other than routine bloods, affected joint aspiration is imperative in the diagnosis of crystal arthropathy and septic arthritis before commencing treatment¹¹. One can find either negatively birefringent needle shaped urate crystals or positively birefringent rhomboid shaped calcium pyrophosphate crystals with leucocytes in the synovial fluid. Serum urate levels are helpful in titrating the urate lowering agents. Full septic screen to exclude infections need to be done before commencing antibiotics.

Radiographs, musculoskeletal ultrasound (US) and magnetic resonance imaging (MRI) are useful in diagnosis as well as monitoring disease activity. Radiographs and MRI especially of the spine and sacroiliac joints help with diagnosis and monitoring ankylosing spondylitis.

TREATMENT :

Multidisciplinary approach is imperative to the treatment of most arthritis. Emphasis should be given on self care. First line treatment with non steroidal provides analgesia. Steroids are used to treat flares in inflammatory arthritis. The second line treatment is with disease modifying drugs (DMARDs) such as methotrexate (MTX), sulphasalazine (SZP), leflunomide (Lef), hydroxychloroquine (HCQ), azathioprine (AZA), mycophenolate mofetil (MMF) and gold. Regular monitoring of the drugs is imperative in the long term treatment of inflammatory arthritis.

The biologics recommended are anti TNF (infliximab (IFX), Adalimumab (ADA), Etanercept (ETA), Certolizumab (CTZ) and Golimumab), Anti B cell (Rituximab (RTX)), Anti IL-6 (Tocilizumab (TCA)) and anti CTLA4 (Abatacept). Antibiotics are essential for septic arthritis treatment. Urate lowering agents are to be commenced with regular titration in recurrent episodes of gout and tophaceous gout.

CASE PRESENTATIONS :

1) A 60 year old lady presented with joint pain and swelling affecting her right knee for 4 months. The pain is worse on activity and she finds climbing stairs difficult. On examination she was tender on her right knee with minimal effusion, crepitus and limited range of movements.

Her investigations revealed

Haemoglobin : 12.0g/dL (11.5-16.4 g/dL)

WCC : $9.0 \times 10^9/L$ ($4-11 \times 10^9/L$)

Platelet : 280 x10⁹/L (150-400 x10⁹/L)
ESR : 20 mm/h (<20 mm/h)
CRP : 7mg/L (0-10 mg/L)
Urea : 8.1 mmol/L (1.7-7.1 mmol/L)
Creat : 130 umol/L (55-125 umol/L)
Rheumatoid factor : Positive

What is the likely diagnosis?

- Rheumatoid arthritis
- Osteoarthritis
- Gout
- Reactive arthritis
- Psoriatic arthritis

2) A 55 year old man presented with sudden-onset pain and swelling in his left knee. The pain is so terrible that he cannot bear the sheets touching his knee. He had history of chronic kidney disease stage 3 and was recently admitted with heart failure. This is his fourth episode and previously his metatarsophalangeal joint, knees and ankle were affected.

On examination he was pyrexial. He had left knee effusion with limited range of movements. Systemic examination was unremarkable.

His investigations revealed

Haemoglobin : 12.5g/dL (11.5-16.4 g/dL)
WCC : 11 x10⁹/L (4-11 x10⁹/L)
Platelet : 460 x10⁹/L (150-400 x10⁹/L)
ESR : 59mm/h (<20 mm/h)
CRP : 45mg/L (0-10 mg/L)
Urea : 5.2 mmol/L (1.7-7.1 mmol/L)
Creatinine : 135 umol/L (55-125 umol/L)
Urine culture : No growth

Which of these is the best test that will aid the diagnosis?

- X ray knee
- Knee aspiration
- Urate levels
- Blood culture
- MRI knee

3) A 35 year old lady presented with 8 week history of joint pain and swelling affecting the MTPs. She complained of significant morning stiffness. On examination, she had synovitis affecting the MTPs.

Her investigations include

Haemoglobin : 11.5g/dL (11.5-16.4 g/dL)
WCC : 11.0x10⁹/L (4-11 x10⁹/L)
Platelet : 540x10⁹/L (150-400 x10⁹/L)
ESR : 40 mm/h (<20 mm/h)
CRP : 21mg/L (0-10 mg/L)
Urea : 6.1 mmol/L (1.7-7.1 mmol/L)
Creat : 79 umol/L (55-125 umol/L)
ALT : 100

Rheumatoid factor : Positive

What is the best way of treating this patient?

- Prednisolone
- Naproxen
- Infliximab
- Cyclophosphamide
- Methotrexate

Answers

- Option b. Osteoarthritis
- Option b. Knee aspiration
- Option e. Methotrexate

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A Young Female with Erythema Nodosum Secondary to Streptococcal Infection

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A 22 year old female presented with seven days history of extensive, painful eruption over bilateral lower limb accompanied by mild fever, sore throat and arthralgia. Clinical examination revealed multiple, round, well demarcated, tender, erythematous edematous plaques on the pretibial area of both legs. The patient had recent history of upper respiratory tract infection. Laboratory test revealed a increased white blood cell count of 11,500/dl with mild Neutrophilia, ESR elevated at 68 mm, Hemoglobin 10.6 gm/dl, C reactive protein positive and anti-streptolysin O titre positive(>200 IU/ml). A search for a number of serum auto-antibodies (anti nuclear antibody, rheumatoid factor, cANCA, pANCA) was negative. Serum ACE level is within normal limit. Skin biopsy was done from left thigh, showed multiple epitheloid cell granulomas with Langhans giant cell reaction in subcutaneous tissues without any evidence of caseous necrosis. So, a diagnosis erythema nodosum was made and underlying etiology was proved to be Streptococcal infection as she had elevated ASO titre. She was treated with oral antibiotic (Amoxycillin-



Clauvulinic acid). Within two weeks of starting of therapy, there was significant improvement and complete disappearance of skin lesions.

Erythema Nodosum is the most frequent clinic-pathological variant of panniculitides. The disorder is a Cutaneous reaction consisting of inflammatory, tender, nodular lesion, usually located on the anterior aspects of the lower extremities. The process may be associated with a wide variety of diseases, being infections, sarcoidosis, rheumatologic diseases, inflammatory bowel diseases, medications, autoimmune disorders, pregnancy and malignancies¹. Treatment of Erythema Nodosum should be directed to the underlying

associated conditions, if identified. Usually, nodules of erythema nodosum regress spontaneously within a few weeks. Systemic corticosteroids are rarely indicated. If a recent streptococcal infection is identified or presumed, a 10 to 14 days course of antibiotic is warranted.

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Anomalous origin of Left Pulmonary artery from Aorta with Tetralogy of Fallot: A case report

N Srivastava*, B Sharma**, P Nandy***

ABSTRACT:

Tetralogy of Fallot is a congenital heart defect which is classically understood to involve four anatomical abnormalities of the heart. Although anomalous origin of the left pulmonary artery is a very entity it is usually associated with tetralogy of Fallot. It is important that the condition be recognized early and especially prior to surgery of tetralogy of fallot. The diagnosis of origin of the left pulmonary artery from the aorta depends on an aortogram, but clinical hints are increased vascularity in the left lung compared with the right lung and a continuous murmur. In this report we describe an adult Tetralogy of fallot associated with anomalous origin of left pulmonary artery, a rare congenital association.

KEY WORDS: *Anomalous pulmonary artery, Tetralogy of fallot, Adult*

INTRODUCTION :

Tetralogy of fallot (TOF) is a complex cyanotic congenital heart disease which includes following principal structural defects: ventricular septal defect (VSD), Infundibular pulmonary stenosis leading to right ventricular outflow obstruction (RVOO), Right ventricular hypertrophy (RVH) and overriding of aorta⁽¹⁾. Variations in structural abnormalities in TOF lead to clinical presentations with variable severity, for instance severity of RVOO may vary, or there may be existence of additional shunts (such as like additional muscular VSD, ductus arteriosus, and major aortopulmonary collateral arteries)⁽²⁾. In this report we describe an adult TOF associated with anomalous origin of left pulmonary artery (AOPA), a rare congenital association.

CASE REPORT :

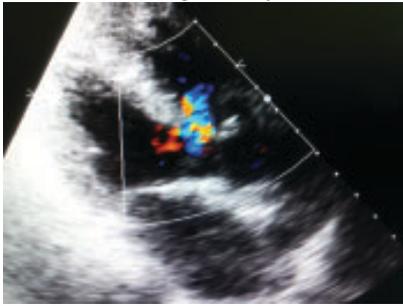
A 22 year old male, resident of Sikkim, India presented to emergency department at CRH with acute abdominal pain of 2 days duration. On initial examination in the emergency room, He was afebrile, his pulse was 102

per minute regular, blood pressure of 110/70 mm Hg, respiratory rate of 20 per minute. He had icterus, central cyanosis, and bilateral clubbing, and absence of pedal edema. His abdomen was rigid with presence of guarding. A provisional diagnosis of acute pancreatitis was made. On further evaluation it was detected that his oxygen saturation was 70% on room air, and 85% with oxygen. Patient reported that he was previously told about presence of some heart disease, but he never had any disabling symptoms, and was not on any therapy. There was no history of cyanotic spells, or recurrent respiratory infections in childhood. In view of central cyanosis, bilateral clubbing and absence of respiratory distress possibility of cyanotic heart disease was considered and medicine consultation was sought.

On further evaluation, previous findings of central cyanosis, and bilateral clubbing were confirmed. His pulse rate was 90 per minute regular, normal in character and no radio-femoral delay. All peripheral pulses were palpable. Blood pressure was 110/70 in right arm supine position, same as in left arm and 120/84 in lower limbs. Tachypnea was absent, neck veins were not distended, there were no respiratory crepts and no edema feet. Cardiovascular examination revealed normally placed apical impulse, no palpable murmurs or thrills, and normal heart sounds. Electrocardiogram showed sinus rhythm, right axis, and absence of any interventricular conduction abnormalities or evidence of ischemia. A chest radiograph was obtained which showed a boot shaped cardiac shadow, absence of cardiomegaly, a homogenous

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Figure 2: Echocardiography showing right ventricular enlargement with right to left shunt.



r a d i o p a q u e parasternal vascular shadow in left second and third intercostal space, plethoric left lung and relatively oligemic right lung fields. (Figure 1) This clinical picture made us suspect TOF, but

lack of severity of symptoms, and chest radiography suggested additional structural defects.

Echocardiography was done, which confirmed VSD, right to left shunt, RVH, and over-riding of aorta. (Figure 2) A 64-slice CECT thorax with CT angiography was done to characterize lesion in left second and third intercostal space, which was a localized pulmonary artery aneurysm. Main pulmonary trunk and right pulmonary artery were hypoplastic. Left pulmonary artery had an anomalous origin from aorta, leading to plethoric left lung field. (Figure 3) A diagnosis of tetralogy of fallot with main and right pulmonary artery hypoplasia with anomalous origin of left pulmonary artery from aorta was made. Patient was discharged from hospital as his acute abdomen resolved, and is doing well on follow up. As there is no cardiothoracic facility in state of Sikkim, he has been referred for surgical correction of the lesion.

Figure 3: 64 slice CT scan and CT angiography reconstructed images showing anomalous origin of left pulmonary artery from aorta.



A) CT angiography image showing Anomalous origin of left pulmonary artery (AOPA).



B) A 3-D reconstruction of 64-slice CT angiography lesion.

DISCUSSION :

In this patient with TOF, there was an anomalous origin of left pulmonary artery from aorta (AOPA). This natural additional shunt minimized symptoms of dyspnea, while cyanosis and clubbing persisted. Patient had remained undiagnosed till adulthood, and was brought to attention, when he was hospitalized due to a concomitant illness.

While TOF is commonest congenital cyanotic heart disease,^{1,2}AOPA is rare. A recent study from a tertiary care cardiothoracic center in India reported only 17 cases of AOPA, over a fifteen year period, and only six of these, all children, had TOF. Three of these six patients with TOF had left sided AOPA, and remaining had right sided AOPA³. Another series of TOF with aortopulmonary collaterals was reported by Ramsay and coworkers from UK, where all such defects were recognized in childhood, and all were surgically corrected. Only adult reported in this series was person where the lesions were recognized in childhood, but he survived till age of 30 years when he was surgically corrected⁴.

The severity of hypoplasia of the RV outflow tract determines severity of TOF. It may vary from mild to complete pulmonary atresia. Pulmonary valve stenosis and supravalvular and peripheral pulmonary arterial obstruction may coexist. Rarely there is a unilateral absence of a left pulmonary artery. In the current era, TOF is almost universally amenable to surgical repair with good long-term outcome. This, however, requires a thorough pre-operative anatomic description of central and branch pulmonary arteries and associated defects, for better surgical planning and a better outcome. Echocardiography with Doppler interrogation gives an accurate diagnosis of intracardiac anatomy of these patients. Cine-angiography, however, compliments the echocardiographic study as it allows more accurate evaluation of pulmonary vasculature, coronary arteries and additional ventricular septal defects. Surgical correction, relieves cyanosis, improves exercise tolerance, and quality of life.^{5,6}

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Acute Myeloid Leukemia : A Rare Cause of Prolonged Pyrexia of Unknown Origin in Elderly

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Abstract

Pyrexia of unknown origin (PUO) is a common clinical diagnostic dilemma. Up to one-third of cases of PUO remain undiagnosed. Infections are the commonest cause of PUO, with tuberculosis (TB) being the commonest infection encountered in India. Acute leukemias, particularly during “blast” transformation, may present as acute fevers in the absence of infection, but are rare causes of PUO. Here we are presenting two cases of prolonged PUO which turned out to be acute myeloid leukemias after ruling out all possible common causes of prolonged pyrexia, mainly based on high index of suspicion and reliable pathological support.

INTRODUCTION:

Pyrexia of unknown origin (PUO) is a common clinical diagnostic dilemma. PUO is defined as a temperature persistently above 38.0 °C for more than 3 weeks, without diagnosis despite initial investigation during 3 days of inpatient care or after more than two outpatient visits. Subsets of PUO are described by medical setting: HIV-related, immunodeficient or nosocomial. Up to one-third of cases of PUO remain undiagnosed.¹ In the elderly, causes of PUO most commonly include malignancy or infection, and less commonly include collagen vascular diseases. Infections were the commonest cause of PUO, with tuberculosis (TB) being the commonest infection encountered in India.^{2,3,4} In the elderly, neoplastic causes of PUO include lymphomas, hepatomas, renal cell carcinomas, and hepatic or central nervous system metastases. Acute leukemias, particularly during “blast” transformation, may present as acute fevers in the absence of infection, but are rare causes of PUO.⁵

CASE 1:

A 75yr male patient presented with h/o prolonged fever since 3 months associated with cough with

expectoration. Fever was low grade, continuous type and not associated with chills and rigors. Cough was not associated with haemoptysis but expectoration which was yellowish in colour, scanty in amount. There was no h/o contact with tuberculosis, high risk behaviour, iv drug abuse or diabetes mellitus. Patient later developed multiple painful nodular lesions over body mainly on thighs, forearms, shin of tibia and face. On examination, patient had pallor, but no icterus, and no lymphadenopathy. Multiple nodular painful lesions were found on body mainly on thighs, forearms, shin of tibia and face. Lesions were reddish in colour and no ulcerations were seen. Chest examination was suggestive of lower respiratory tract infection. Cardiovascular, Nervous system and per abdomen examination was within normal limits.

Initial routine lab investigations revealed Hb -6.9g/dl, TC-1300/mm³; DLC- Neutrophils-18, lymphocyte-78, monocytes-2, eosinophils-2. ESR-124mm AEFH, urine RE-NAD, RBS-95, Creatinine-0.7mg/dl, CXR(PA view)- consolidation of rt lower lobes, sputum for AFB- neg, sputum c/s- gram positive cocci sensitive to piperacillin tazobactam, ciprofloxacin, ofloxacin, imipenem., USG abdomen-NAD, MP optimal-neg, WIDAL titre- non suggestive, montoux test- neg, HIV-Neg, HbSAg-neg, anti-HCV- neg. Patient was started on imipenem, fluconazole keeping in mind the c/s reports and neutropenia

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of the patient. Patient showed no improvement after 2 weeks of antibiotics and the skin lesions remained and newer ones erupted.

Biopsy from the skin lesions showed oedematous stroma with lymphocyte infiltration with marked perivascular infiltration of lymphocytes with fibrinoid necrosis of blood vessels suggestive of vasculitis. ANA-neg, serum ADA-15u/l. On repeat CT scan of thorax showed no resolution in pneumonia and on repeating the hemogram, hb-8gm/dl, rbc-2.45 million/mm³, TC-2600/mm³, DLC- neutrophils-5, lymphocytes-22, atypical blasts cells-73%. platelets-25000/mm³. Serum electrophoresis for M band was negative. Due to appearance of atypical cells in periphery, bone marrow examination was carried out. Bone marrow examination showed blast cells of myeloid origin >30% suggestive of AML-M2 (aleukemic leukemia). This could explain the persistent

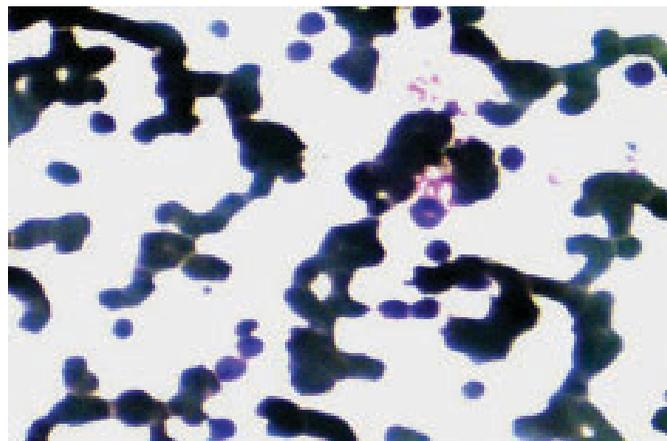


neutropenia, non resolving pneumonia, prolonged fever and skin lesions (erythema nodosum).

CASE 2:

A 54 yr male patient presented with fever for 2 months which was gradual in onset and low intensity continuous type of fever. There was no diurnal variation and not associated with chills and rigors, relieved by medications temporarily. Fever was associated with dry cough and a mild chest discomfort. Cough was non productive in nature, gradual in onset and non progressive, with no diurnal or postural variation. Patient also complains of low back ache since 2 months. This was gradual in onset and progressive in nature. Pain is of low grade. There is no h/o trauma, tuberculosis or any surgeries. On examination, pallor was present, no icterus or lymphadenopathy or clubbing was found. Chest, cardiac, abdomen and CNS examinations showed no obvious abnormalities. On routine lab examinations, haemoglobin-8.7gm%, TC- 5,110, DLC showed neutrophils-12%, lymphocytes-73%, monocytes-6%, eosinophils-2%, atypical cells-5%. ESR-130mm AEFH, platelets-60000/mm³. RE urine-NAD, Urine c/s-

sterile, s.electrophoresis for M band – neg. MP optimal-neg, WIDAL titres – normal, HIV-neg, HbS Ag-neg, Anti HCV- neg. Chest xray- normal, usg abdomen- normal. We performed bone marrow examination because of atypical cells in periphery and long standing backache. Bone marrow examination reports showed picture suggestive of AML M2 in evolution with blast around 25%.



DISCUSSION :

Prolonged febrile illnesses still remains a diagnostic challenge. Despite the technological progress in diagnostic approach, the origin of the fever remains elusive in many patients, especially in those with episodic fevers. Non-infectious inflammatory diseases emerge as the most prevalent diagnostic category, especially in elderly.⁶ Infections were the commonest cause of PUO, with tuberculosis (TB) being the commonest infection encountered in India.^{2,3,4}

WESTERN STUDIES⁶

CAUSE OF PUO	% OF CASES
INFECTIONS	25
TUMOURS	12
MULTISYSTEM DISORDERS (encompassing rheumatic diseases, connective tissue disorders, vasculitis including temporal arteritis, polymyalgia rheumatica, and sarcoidosis)	31

INDIAN STUDY⁷

CAUSES OF PUO	% OF CASES
INFECTIONS (TB most common)	50
MALIGNANCY (lymphoma- most common)	12.5
COLLAGEN VASCULAR DISEASE	7
NO CONCLUSIVE DIAGNOSIS	9

Haematological malignancies are among the rare causes of Prolonged febrile illnesses mainly in elderly.

Acute myeloid leukemia (AML) is a malignant stem cell disorder characterized by a disruption in haematopoiesis resulting in accumulation of immature or blast cells in the bone marrow and the peripheral blood. This leads to bone marrow failure, severe cytopenias and death if left untreated. The incidence of AML increases with age, with the majority of patients older than age 60. Elderly patients with AML have a particularly poor prognosis.⁸

Patients with AML usually present with symptoms related to their cytopenias. They can develop fevers or infections as a result of neutropenia. Anaemia can sometime lead to rapidly progressing weakness and fatigue. Patients may notice petechiae or easy bruising or bleeding due to thrombocytopenia. When they present to their physician with these symptoms or when routine lab work is done (complete blood count), these abnormalities may be identified. Further testing to diagnose AML can include examination of the peripheral blood smear, bone marrow aspirate and biopsy, cytogenetic and molecular analysis, and immunophenotyping.⁹

Patients with AML often have decreased neutrophil levels despite an increased total white blood cell (WBC) count. Patients generally present with fever, which may occur with or without specific documentation of an infection. Patients with the lowest absolute neutrophil counts (ANCs) (ie, < 500 cells/ μ L, especially < 100 cells/ μ L) have the highest risk of infection. Patients often have a history of upper respiratory tract infection symptoms that have not improved despite empiric treatment with oral antibiotics. Physical findings other than bleeding and infection may include organomegaly, lymphadenopathy, sternal tenderness, retinal haemorrhages, and infiltration of gingivae, skin, soft tissues, or meninges (more common with monocytic variants M4 or M5).

In Elderly, AML may be secondary to progression of a myelodysplastic process or a chronic bone marrow stem cell disorder, such as polycythemia vera, chronic myelogenous leukemia, primary thrombocytosis, or paroxysmal nocturnal hemoglobinuria.¹⁰

Although acute leukemia can present with tumour fever, the most common cause of fever in patients with

acute leukemia is infection. Thus all cases of febrile neutropenia suspected to be due to acute leukemias should be considered due to infection itself and started with broad spectrum antibiotics.

This case report thus enlighten us about the possibilities of rare causes of pyrexia of unknown, in the elderly, which can be diagnosed only by high index of suspicion of haematological malignancies. In our Indian context the major cause of PUO in elderly is reported to be infections, mainly tuberculosis, in contrast to this here we have presented two cases of PUO in elderly having haematological malignancies (acute myeloid leukemia). Therefore, in the diagnosis of PUO in elderly, haematological malignancies should also be considered as a cause of prolonged pyrexia.

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Pancoast Tumor Resulting in Complete Brachial Plexopathy : A Case Report

B Hazarika*, S Sharma**, C S Metage***, J Sarma****, K R Sarmah*****,

ABSTRACT :

Pancoast tumor is a primary carcinoma occurring at the lung apex. Because of such anatomical location these tumors have a distinct clinical presentation called pancoast syndrome, presents as a severe pain in neck, shoulder, arm and Horner's syndrome. The pulmonary symptoms of the lung cancer are rather rare. Here we report a case 42yr old male who presented with pain in back, right shoulder and arm along with weakness and numbness in forearm and hand. On further evaluation he was diagnosed of having pancoast tumor. This report demonstrates a case of pancoast tumor presenting with features resulting from involvement of brachial plexus.

KEY WORDS : *Pancoast tumor, pancoast syndrome, Horner's syndrome, brachial plexopathy*

INTRODUCTION :

Pancoast tumors are a unique subset of lung carcinomas, which are located in the apex of lung and invade the tissue in continuous with the apical chest wall and the structures of thoracic inlet (parietal pleura, 1st & 2nd ribs, 1st & 2nd vertebral bodies, lower nerve roots of brachial plexus, the sympathetic chain and stellate ganglion, the subclavian vein & artery) resulting in a clinical picture known as pancoast syndrome.¹ Majority of patients present with neuro-musculoskeletal symptoms such as pain arising in chest wall or shoulder which may radiate to neck and arm, Horner's syndrome and weakness and atrophy of forearm and hand muscles resulting from invasion into the C8 and T1 roots of the brachial plexus. More infrequent manifestations include supraclavicular adenopathy, superior vena cava syndrome, and involvement of the phrenic or laryngeal nerves². This case illustrates the clinical features consistent with complete brachial plexopathy along with other features of pancoast

syndrome caused by squamous cell carcinoma of lung.

CASE REPORT :

A 42yr old farmer presented with aching pain in back of chest on right side with radiation to right shoulder, neck and right upper limb to a local physician who diagnosed him as a case of cervical spondylosis and put on conservative management. During the course of treatment his pain became severe with development of weakness along with numbness and tingling sensation in whole of the right upper limb, more severe on the inner side of hand. The patient was then referred to the Department of Pulmonary Medicine, Gauhati Medical College and Hospital, Assam for further evaluation. Upon further questioning the patient stated that he had disturbed sleep due to pain. He had no underlying disease, no trauma or surgery before symptoms occurred. He had no other respiratory complaints except chest pain. He was chronic smoker (18-20 beedies/day) for 25yrs. His blood pressure was 120/70mmHg, pulse rate 80bpm & respiratory rate 20cycles/min. Horner's syndrome (ptosis, miosis and anhydrosis) was detected on the right side (Fig:1) and supraclavicular fullness was noted on right side which on examination showed a diffuse nodular non-tender swelling. Active neck movements were normal and did not aggravate pain. There was loss of contour and atrophy noted in arm, forearm and thenar & hypothenar eminence

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Fig:1 Horner's syndrome on right side.

of hand on right side. Full passive range of movements revealed flaccid tone at the shoulder, elbow and wrist on right side.

Muscle power testing revealed grade 3/5 at shoulder joint, elbow, wrist and all small muscles of hand on right side. Muscle stretch reflex examination showed hyporeflexia of biceps jerk, supinator reflex and absent triceps jerk on right side. Diminished sensations to fine touch and pin prick seen in right upper limb, profound loss at ulnar side of arm and forearm. Normal power, reflex and sensations present in left upper limb and both the lower limbs. Respiratory system examination revealed right supraclavicular fullness which was dull on percussion and decreased breath sounds in

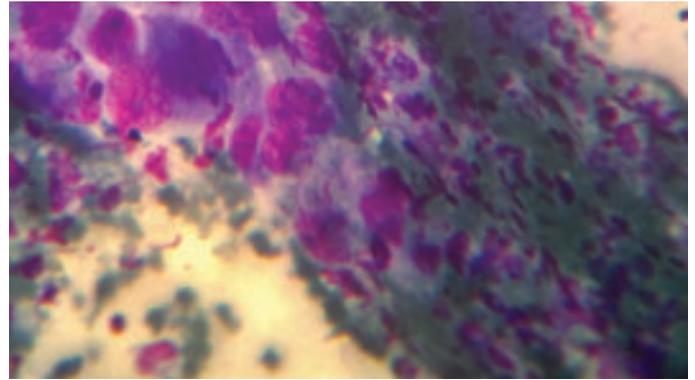


Fig: 4 Photomicrograph of FNAC from right upper lobe mass showing malignant looking epithelial cells with large hyperchromatic nuclei and eosinophilic cytoplasm arranged in clusters and in sheets, features suggestive of undifferentiated squamous cell carcinoma.

carcinoma (Fig: 4). Nerve conduction studies showed absent sensory response for right radial, median and ulnar nerves. The patient was referred to oncolog centre for further management.

DISCUSSION :

Pancoast tumours account for approximately 2-5% of all lung cancers and are most commonly of bronchogenic origin³. The highest occurrence is found in men over 50 years of age (peak incidence between 40 and 60 years of age), with a history of cigarette smoking⁴. The initial symptoms of Pancoast tumours are musculoskeletal in nature. In fact, more than 90% of patients first present with shoulder pain, rather than with pulmonary symptoms^{3,4}. Pulmonary symptoms are rarely seen in these patients because the bulk of the tumor is extra pulmonary leaving the underlying lung parenchyma unaffected except in most advance cases. Instead the tumor invades the narrow thoracic inlet involving the structures like lower nerve roots of brachial plexus, sympathetic nerve, subclavian artery and vein which become susceptible to compression and traction forces arising due to the tumor growth resulting in pancoast syndrome. The pancoast tumor typically consists of severe pain in the shoulder, scapula and medial side of the arm along with Horner's syndrome. Initially the patient may suffer only from nagging pain in the shoulder and on medial end of scapula due to irritation of parietal pleura as the tumor grows and invades the surrounding structures the other components of syndrome come into clinical picture. The expanding tumour may erode 1st & 2nd ribs, vertebral bodies and may eventually lead to cord compression and myelopathy. The



Fig: 2 Chest xray of the patient showing homogenous opacity in right upper zone

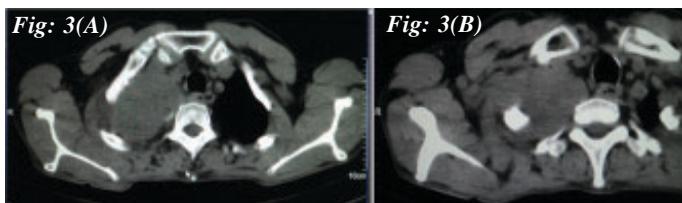


Fig:3: CT thorax showing tumour in Right Apical region involving the 1st rib (A) , and tumour compressing the roots of brachial plexus (B).

right apical regions. The patients clinical findings were consistent with complete right brachial plexopathy. Chest radiograph showed a homogenous opacity in the right upper zone (Fig: 2).CT thorax showed mass lesion in right upper lobe with involment of the first rib (Fig:3A) and compression of the brachial plexus on the right side (Fig:3B). FNAC from the right supraclavicular swelling showed features suggestive of poorly differentiated type of squamous cell

pulmonary symptoms are rare except for supra clavicular fullness and auscultatory abnormality. The above mentioned clinical features will become evident only in the advance stages of the disease. However earlier detection or suggestion of the disease can be made by chest radiographs. Chest radiograph showed peripherally located and characterized by a spiculated density in the apices of the lung with or without evidence of mediastinal abnormality. Percutaneous needle biopsy via ultrasound or under computerized tomography (CT) guidance is generally sufficient to make the diagnosis. Preoperative radiotherapy followed by extended surgical resection has been the most common treatment of pancoast tumors⁵.

CONCLUSION :

A diagnosis of Pancoast tumour should always be considered in middle-aged patients who present with complaints of persistent shoulder and arm pain and a

history of smoking. Early diagnosis is important as prognosis is directly dependent on quick and prompt treatment.

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A Case of Invasive Mycosis Presenting with Cavernous Sinus Thrombosis

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ABSTRACT :

Mucormycosis refers to an infection with fungi of the Mucoraceae family. The major pathogens in this group are of the genera *Rhizopus*, *Absidia*, *Mucor*, and *Cunninghamella*. They are found throughout the world and they grow in soil and decaying vegetable matters. Less than 5 per cent of cases occur in normal hosts. Seventy per cent occur in diabetics who become acidotic, and also acidosis from other conditions can predispose to development of rhinocerebralmucormycosis. The spores are inhaled or inoculated through damaged skin or mucosa. An acute suppurative pyogenic necrosis is produced with granuloma formation if the process is more chronic. These fungi have an affinity for arteries which they penetrate, producing thrombosis and infarction and even causing distal embolization with the formation of true mycotic aneurysms. Central Nervous System disease occurs in about one-third of cases and the portal of entry is by the bloodstream or by contiguous spread from palate or paranasal sinuses and from orbit [1]. Hence we are reporting a case of invasive mycosis presenting with cavernous sinus thrombosis.

KEY WORDS : Mucormycoses, Rhinocerebral

INTRODUCTION :

Rhino-cerebralmucormycosis is a rapidly progressive opportunistic infection predominantly affecting the immunocompromised people. Aspergillosis and zygomycosis are mainly responsible for Central Nervous System mycosis. Mucormycoses are a group of invasive infections caused by filamentous fungi of the Mucoraceae family. The rhinocerebral form of the disease being the most common in large case series. The fungus destroys the tissue of the nasal passages, sinuses, or hard palate, producing a black or pus filled discharges and visible patches of dying tissue. The patient will typically have fever, pain, and proptosis. The fungus then invades the tissues around the eye socket and eventually the brain. At that point the patient may have convulsions or paralysis on one side of the body.²

CASE REPORT :

A 55 year male diabetic patient, Mr Debananda Saikia, hailing from Amuguri, Sivasagar was admitted in

Assam Medical College & Hospital in March 2014, with complaints of severe frontal headache radiating to back with sudden onset of diminished vision of the right eye and facial deviation towards the left, associated with fever and chill. He was admitted in the Department of Medicine and started with conservative treatment.

On examination there was proptosis of right eye followed by the left eye. The eyes were congested with restriction of movement. There was associated palsy of right lateral gaze with deviation of eyes towards the left indicating abducent nerve (cranial nerve VI) palsy. There was Lower Motor Neuron type of facial nerve palsy of the right side.

The tongue was found to be deviated towards the right indicating right hypoglossal nerve involvement without atrophy or fasciculation of the tongue. There was difficulty in deglutition with loss of pharyngeal reflexes. Motor system examination of both upper and lower limbs revealed normal findings.

Preliminary work up of the patient revealed a high random sugar level (340 mg/dl) with raised HbA1c level (7.4%) and raised total count (13,500) with predominantly neutrophilia. Other blood biochemical profiles were found to be normal. NECT brain revealed diffuse atrophy of brain. CSF analysis was done which revealed lymphocytosis, a raised protein level (85 mg) with a normal

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sugar level . CSF ADA was 13. Assuming to be a case of tuberculosis, antitubercular treatment was started empirically.

The condition of the patient however deteriorated, with increasing proptosis. Neurology opinion was taken. Considering the case to be of invasive mucormycosis, a MRI of brain with nasal sinuses were done .The MRI was suggestive of infiltrative rhinocerebralmycosis causing right sided cavernous sinus thrombosis with focal meningitis along right CP angle cistern, right parapontine cistern associated with non enhancing T2/FLAIR hyperintense lesion in right paramedian pons. So the diagnosis of invasive mycosis was confirmed. Intravenous Amphotercin B (lyophilised) 150 mg/day was given for 7 days. The clinical condition improved and the patient was discharged. The case is now on follow up.



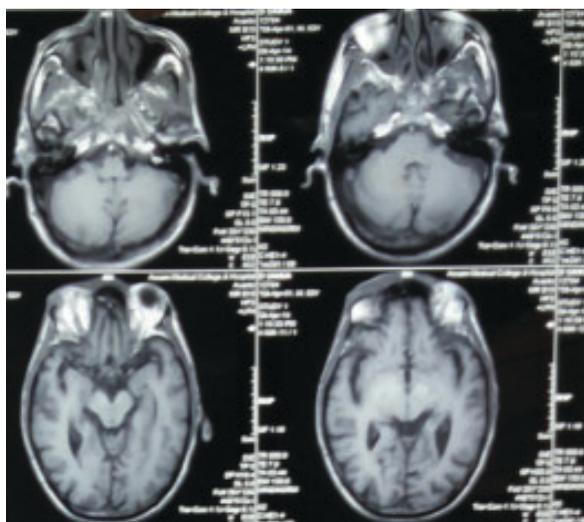
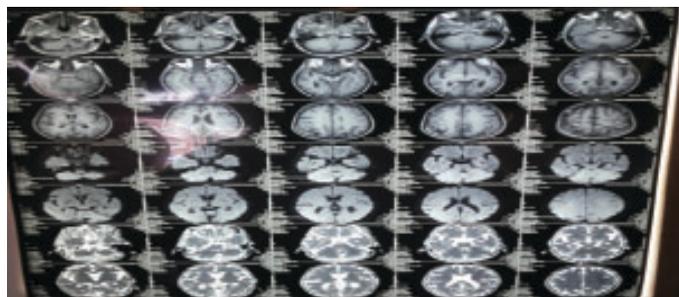
DISCUSSION :

Mucormycosis represents a group of life-threatening infections caused by fungi of the order Mucorales. Mucormycosis is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality (>40%) than many other infections. A high index of suspicion is crucial for diagnosis, initiation of therapy, often before confirmation of the diagnosis, is necessary to optimize the outcomes.²

The classical presentation is of painful proptosis associated with visual loss in a diabetic. The fungus then extends by the venous system into adjacent brain. Nasal ulcers and cutaneous necrosis are not uncommon. The patient is ill and there is usually pyrexia. As contiguous cranial nerves are picked off, multiple palsies occur and infarction of blood vessels leads to focal neurological deficit. Abscesses distant from the site of local infection may be set up and cause confusing localizing signs. Progression of the disease is rapid and secondary infection may occur.¹

Mucormycosis can be divided into at least six clinical categories based on clinical presentation and the involvement of a particular anatomic site: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. These categories of invasive mucormycosis tend to affect patients with specific defects in host defense. Rhinocerebral mucormycosis continues to be the most common form of the disease. Most cases occur in patients with diabetes, although such cases (probably due to glucocorticoid use) are increasingly being reported in the transplantation settings.²

The initial symptoms of rhinocerebral mucormycosis are nonspecific which include eye or facial pain and facial numbness followed by the onset of conjunctival suffusion, blurred vision, and soft tissue swelling. Fever may be absent in up to half of the cases, while white blood cell counts are typically elevated as long as the patient has



functioning bone marrow. If untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in compromise of extraocular muscle function and proptosis, typically with chemosis. Onset of signs and symptoms in the contralateral eye, with resulting bilateral proptosis, chemosis, vision loss, and ophthalmoplegia, are ominous and suggests the development of cavernous sinus thrombosis.

The successful treatment of mucormycosis requires four steps: (1) early diagnosis; (2) reversal of underlying predisposing risk factors, if possible; (3) surgical debridement; and (4) prompt antifungal therapy. Starting dosages of 1 mg/kg per day for AmBdeoxycholate and 5–7.5 mg/kg per day for liposomal AmB (LAmB) and amphotericin B lipid complex (ABLC) are commonly given to adults and children. Whether higher dosages provide any additional benefit is unclear. However, dose escalation of LAmB to 10 mg/kg per day for CNS mucormycosis may be considered in the light of the limited penetration of polyenes into the brain. ABLC dose escalation above 7.5 mg/kg per day is not advisable given the lack of relevant data.

The roles of recombinant cytokines and neutrophil transfusions in the primary treatment of mucormycosis are not clear. Limited data indicate that hyperbaric oxygen may be useful in centers with the appropriate technical expertise and facilities [2]

In general, antifungal therapy for mucormycosis should be continued until all of the following objectives are attained: (1) resolution of clinical signs and symptoms of infection; (2) resolution or stabilization of residual

radiographic signs of disease on serial imaging; and (3) resolution of underlying immunosuppression. For patients with mucormycosis who are receiving immunosuppressive medications, secondary antifungal prophylaxis is typically continued for as long as the immunosuppressive regimen is administered.^{2,3,4}

CONCLUSION :

Cerebral Mucormycosis is no longer a rare disease. Apart from Immunodeficiency states, dirty sanitation and hygiene are also responsible for this life threatening condition. High degree of suspicion is very essential.

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